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BAGASSE DISEASE OF THE LUNGS

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NEW ORLEANS

Bagasse is the product remaining after extraction of sugar from sugar cane. This material is commonly baled and if not used immediately may remain exposed in the field for some months before being converted, by processing, into insulating and acoustic board. Workers employed in the breaking of these bales sometimes acquire a respiratory illness. Seven cases of such a reaction have been reported.[1] In order to clarify the clinical picture and course of this disturbance, we are summarizing, aside from the 7 reported cases, 11 of our own. The following 2 histories are given in detail to bring out some of the difficulties in the evaluation of possible etiologic factors.

REPORT OF CASES

CASE 1.—J. N., a white youth aged 18, entered the hospital on Oct. 2, 1942, complaining of shortness of breath of one week's duration. He had been working for one month in an industrial plant handling bales of bagasse. The onset of the shortness of breath was acute, but the patient continued to work that day and the following day, finally being forced to rest by the progressively more severe dyspnea. There was a slight cough producing mucoid sputum. No hemoptysis was noted. The systemic review revealed nothing of note. At the time of his admission the temperature was 100.6 F., the pulse rate 112 per minute, the respiratory rate 56 per minute and the blood pressure 120 systolic and 70 diastolic. Aside from the profound dyspnea, the patient did not appear acutely ill. The chief physical findings were limited to the chest and were as follows: unimpaired respiratory excursion and motion, unimpaired tactile and vocal fremitus, normal resonance and bronchovesicular to bronchial breathing over the lower left quadrant of the chest posteriorly. No rales or rubs were heard.

An examination of the blood on admission revealed 75 per cent (12 Gm.) hemoglobin, 4,700,000 red cells and 15,040 white cells, consisting of 90 per cent polymorphonuclear cells, 8 per cent lymphocytes and 2 per cent monocytes. The hematocrit reading was 46 per cent. The sedimentation rate was 35 mm. per hour (Wintrobe, corrected). Urinalysis gave essentially normal results on several occasions. Additional studies of the blood revealed 9.1 mg. of urea per hundred cubic centimeters, dextrose (fasting) varying from 108 to 93 mg. per hundred cubic centimeters, a carbon dioxide–combining power of 44 volumes per cent, alkaline phosphatase 4.4 Bodansky units and phosphorus 4.2 mg. per hundred cubic centimeters. Kline and Kolmer tests gave negative results. Culture of blood and agglutination tests for typhoid, undulant fever, typhus and tularemia also gave negative results. Examinations of the sputum for acid-fast bacilli, fungi and other organisms repeatedly failed to reveal any, except for the presence of Monilia on one occasion. The reaction to the Mantoux test was negative with a concentration of 1:100 of old tuberculin.

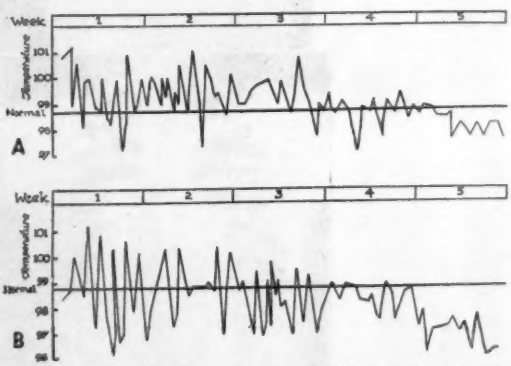

Fig. 1.—Temperature charts of patients 1 (chart *A*) and 2 (chart *B*), showing the febrile course of the disease during the stay in the hospital.

The Frei test and brucellergen cutaneous tests gave negative results.

Roentgen examination of the chest on the patient's admission revealed diffuse, fine infiltration throughout both lungs. The course of this infiltration is shown in serial roentgenograms reproduced in figure 2.

During observation in the hospital the patient manifested for three weeks an intermittent fever, reaching its peak late in the afternoon (fig. 1 *A*). The pulse rate was constantly elevated above 100 per minute, often attaining 115. The respiratory rate remained elevated, once reaching 80 per minute. On the day after admission, the patient had hemoptysis of small amount, which subsided quickly.

Therapy in the initial weeks was chiefly supportive, with a high caloric diet. On October 27 administration of potassium iodide, in doses totaling 37 grains (2.4 Gm.)

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1. (*a*) Jamison, C., and Hopkins, J.: Bagasscosis: A Fungus Disease of the Lung, New Orleans M. & S. J. **93**:580-582 (May) 1941. (*b*) Castleden, L. I. M., and Hamilton-Paterson, J. L.: Bagassosis: An Industrial Lung Disease, Brit. M. J. **2**:478-480 (Oct. 24) 1942. (*c*) Gillison, J. A., and Taylor, F.: Four Cases of Bagassosis, ibid. **2**:577-578 (Nov. 14) 1942.

daily, was begun, and this was continued until the patient was discharged. After the institution of this therapy the temperature curve remained within normal limits, the pulse rate gradually slowed to an average level of 80 per minute and the respirations within two weeks slowed to an average of 25 per minute. Subjectively and objectively the patient was greatly improved. Dyspnea disappeared. Physical examination continued to reveal a paucity of abnormalities. No rales were heard at any time, and bronchovesicular and suppressed breath sounds of slight degree were heard in the lower left quadrant of the chest posteriorly.

On November 17 the patient's blood showed a red cell count of 6,000,000, 85 per cent hemoglobin (Sahli) and a white cell count of 13,560, with 73 per cent polymorphonuclear cells, 16 per cent lymphocytes, 7 per cent monocytes and 4 per cent eosinophils; the sedimentation rate was 54 mm. per hour (Wintrobe, corrected). The hematocrit reading was 48 per cent. A week later the sedimentation rate was 65 mm. per hour (Wintrobe, corrected) and the red cell count was 6,100,000.

The patient stated that he had weighed 140 pounds (63 Kg.) prior to beginning work with bagasse. At the time of admission to the hospital he weighed 114 pounds (51.3 Kg.), a loss of 26 pounds (11.7 Kg.), according to the history, within one month, and during the ensuing three and a half weeks before iodide therapy was started he continued to lose steadily, his weight dropping to 109 pounds (49 Kg.). With the administration of iodides gain in weight began, and it continued steadily until, at the time of discharge, on November 25, the patient weighed 117½ pounds (52.9 Kg.).

On the day of discharge, the patient had a normal electrocardiogram, and fluoroscopic examination of the heart and great vessels showed them to be normal. The vital capacity was repeatedly 1,700 cc., a deviation of 60 per cent minus (Wilson) from the normal for the age, height and weight of the patient. The roentgenologic examination showed little change in the lesions in the chest. The physical examination revealed no abnormalities, and there were no subjective complaints. The hematocrit reading at the time was 42 and the red blood cell count 6,190,000. The hemoglobin content was 112 per cent, or 16.3 Gm. per hundred cubic centimeters.

A follow-up examination on Dec. 21, 1942, approximately one month after the patient's discharge, showed a gain in weight to 121 pounds (54.5 Kg.). There was slight dyspnea on mild exertion but none at rest. Cough was infrequent, with a small amount, less than a teaspoon, of yellow sputum expectorated in the morning. The lungs appeared clear on physical examination but not in roentgenograms, although some clearing was reported (fig. 2). The temperature was 99.4 F., and the pulse and the respiratory rate were 80 and 21 per minute, respectively. The vital capacity had increased to 2,050 cc. The sedimentation rate and the white cell count of the blood were normal, but the hemoglobin content was still high, 140 per cent. Later a roentgenogram (fig. 2) showed complete clearing.

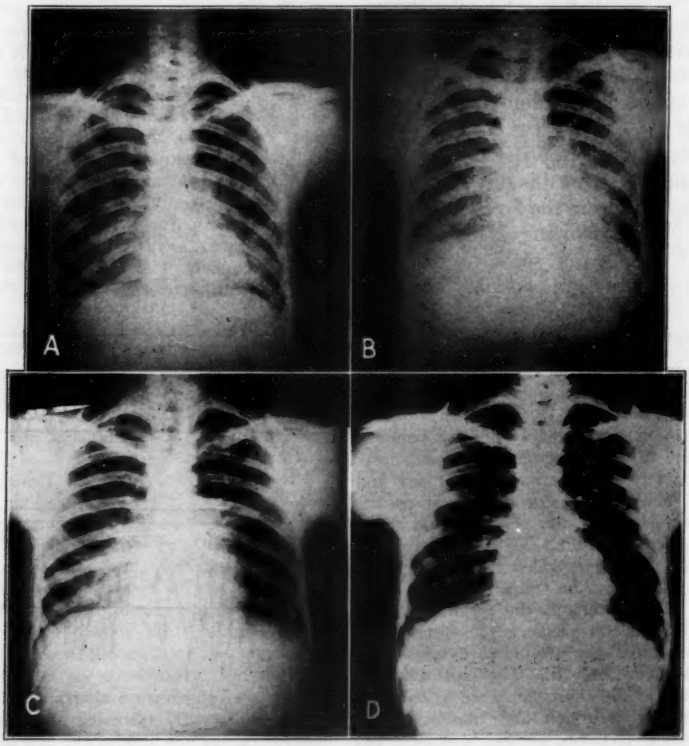

Fig. 2.—Roentgenograms of the chest of patient *1*, taken (*A*) on admission, (*B*) the following day, (*C*) five weeks and (*D*) eleven weeks later. The last plate (*D*) shows complete resolution.

CASE 2.—F. T., a 46 year old white man, married, entered the hospital on Sept. 23, 1942, complaining of tightness in the chest, dyspnea and a sense of smothering. The onset had been gradual, and these symptoms had

continued to grow worse. Two weeks prior to admission, the patient began to have chills at night followed by severe drenching sweats which saturated the bedclothes. He believed that fever was present but was unable to measure it. These symptoms continued until a week prior to his admission to the hospital. Dyspnea on exertion was severe, forcing him to lie down to rest. A mild, unproductive cough had been present since the onset. No hemoptysis or foul-smelling sputum was noted. In seven months the patient lost 10 pounds (4.5 Kg.).

The patient stated that he had been a farmer all his life. Three weeks prior to admission he began to work in an industrial plant breaking bagasse with a pick. He stated that there was not much dust and that he did not wear a mask but did keep a rag over his nose and mouth all the time he was working.

At the time of admission the patient did not appear acutely ill. The temperature was 98.2 F., the pulse rate 100 per minute, the respiratory rate 22 per minute and the blood pressure 108 systolic and 76 diastolic. No generalized lymphadenopathy could be demonstrated. The physical examination revealed no abnormalities on admission.

A blood count at the time the patient entered the hospital revealed 4,600,000 red blood cells, 70 per cent hemoglobin (11.2 Gm.), 7,400 white blood cells, 80 per cent polymorphonuclear cells, 15 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. The sedimentation rate was 1.4 mm. per minute (Rourke-Ernstene) and 40 mm. per hour (Wintrobe, corrected). The hematocrit reading was 48.5 per cent, and the white cell count a week later was 13,350, with 102 per cent hemoglobin (14.9 Gm.) per hundred cubic centimeters. Urinalysis repeatedly gave results within normal limits. The reactions to Kline and Kolmer tests were negative. Additional studies of the blood revealed 11.1 and 12.9 mg. of urea per hundred cubic centimeters, 95 and 91 mg. of dextrose per hundred cubic centimeters (fasting values) and a carbon dioxide–combining power of 40 volumes per cent on admission and 50 volumes per cent three weeks later. The calcium content of the blood was 7.7 and 8.3 mg. per hundred cubic centimeters the phosphorus content, 4.1 mg. The value for alkaline phosphatase was 1.7 Bodansky units. The result of the Frei test was negative. The Mantoux test elicited a 2 plus reaction with a concentration of old tuberculin of 1:10,000. Culture of the blood gave negative results, as did agglutination tests of the blood for typhoid, typhus, undulant fever and tularemia. Studies of the sputum for acid-fast bacilli and for fungi repeatedly failed to reveal any. The result of the brucellergen test was negative.

The roentgenologic report on the patient's admission showed diffuse mottled infiltration throughout both pulmonary fields. Serial roentgenograms taken during his stay in the hospital are shown in figure 3.

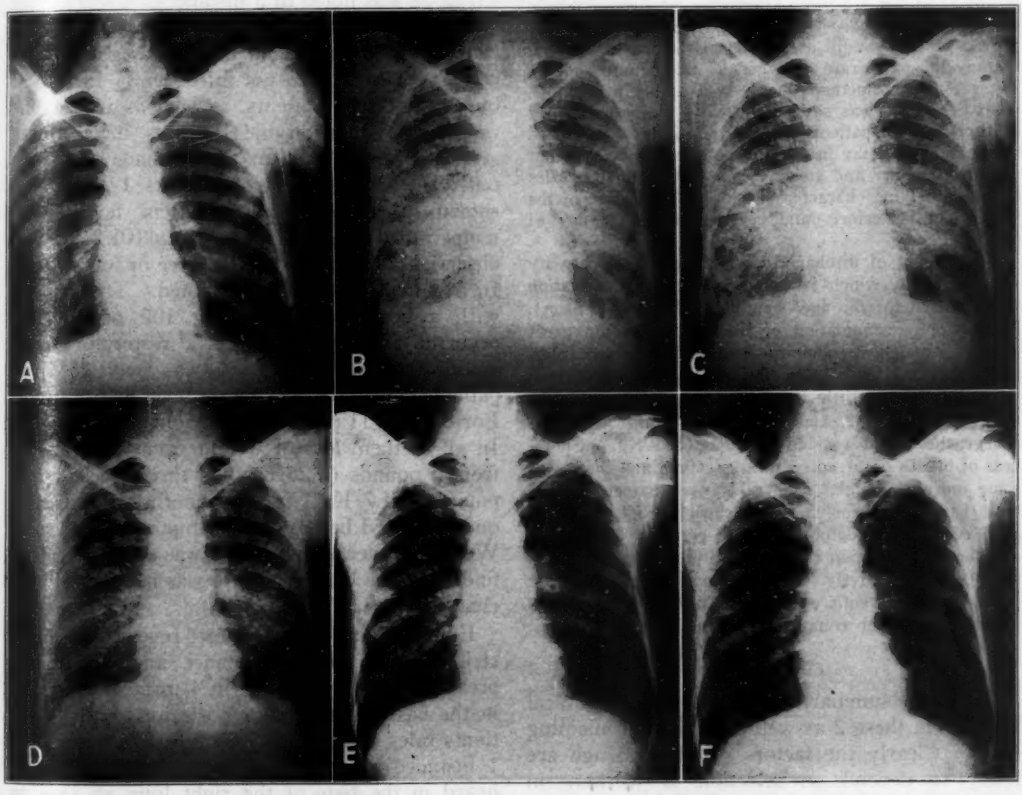

Fig. 3.—Roentgenograms of the chest of patient 2, taken (*A*) on admission, (*B*) two weeks later and (*C*) to (*F*) over the succeeding four month period. Note the increasing infiltration from (*A*) to (*B*) and the gradual but not complete resolution from (*C*) to (*F*).

On the day of admission the patient weighed 115 pounds (51.75 Kg.), and during the ensuing four weeks the weight varied from 113 to 117 pounds (50.9 to 52.7 Kg.). For the first two weeks in the hospital the patient manifested an irregular, intermittent fever, the temperature reaching 101.2 F., which gradually receded so that the temperature returned to normal by the end of the third week (fig. 1*B*). The pulse rate for the first four weeks of hospitalization averaged 100 per minute, but it fluctuated considerably, once attaining 120 per minute. During the febrile episodes the respirations averaged 30 to 40 per minute, once reaching a level of 45.

At the end of the fifth week of hospitalization, potassium iodide therapy was begun, with a total dose of 37 grains (2.35 Gm.) a day. Thereafter, no further febrile episodes were noted. The pulse and the respirations improved gradually until at the end of the fourth week of therapy the pulse rate averaged 95 per minute and the respiratory rate fluctuated between 20 and 30 per minute. Gain in weight was slow and steady until on the day of discharge, the patient weighed 122 pounds (54.9 Kg.). Throughout his stay in the hospital the subjective complaints gradually and steadily improved, although rales of fine, crackling character developed in the base of the right lung posteriorly and persisted until the day of discharge.

On the day of discharge the patient's vital capacity was 1,555 cc., which is minus 60 per cent deviation from normal for the age, weight and height (Wilson). Fluoroscopic examination of the heart and the great vessels revealed no abnormalities. The electrocardiogram was within normal limits. The roentgenogram showed relatively little improvement.

On Dec. 21, 1942, approximately a month after discharge, the weight was 126½ pounds (56.9 Kg.). Shortness of breath occurred on mild exertion, and there was some morning cough. Fine rales were numerous over both bases posteriorly. Vital capacity had risen to 2,000 cc. The hemoglobin was 123 per cent (17.8 Gm.) and the sedimentation rate and white cell count 18 mm. and 4,850 respectively. A roentgenogram of the chest taken in the eleventh week of the disease showed considerable, but not complete, clearing (fig. 3).

COMMENT

The table summarizes the outstanding clinical findings in these 2 as well as in the 9 remaining cases. Clearly the factors of sex and age are likely to depend on selection of workers in bagasse on the basis of ability to perform manual labor. Hence, all the patients were men, and their ages averaged 27 years. Six were white, and 5 were Negro. The length of exposure to bagasse dust before symptoms arose was known in 8 cases and varied from three weeks to two years. A clearcut history of exposure for only three weeks to two months was obtained in 3 of these cases. In Gillison and Taylor's cases this period was from two to four months.[1e]

The symptomatic picture was variable but showed several rather constant characterizing features. Cough and dyspnea were early and important symptoms. Dyspnea occurred in all and was almost invariably the presenting complaint. Characteristically it appeared suddenly and became sufficiently severe within a few days to force the patient to rest. Cyanosis was noted but once. Cough occurred in all instances. Hemoptysis was noted 4 times; it was of short duration (several days) and the amount of blood varied, not exceeding a teaspoon daily. In general the sputum, which was raised in 9 instances, was scant and mucoid. It had a whitish appearance except when blood tinged. Others[1e] have described the sputum as dark and yellow, dirty and foul smelling. None of our patients described the sputum in these terms. Pharyngeal irritation was noted in 3 instances. Pleural pain was not observed but retrosternal pain was associated with dyspnea and cough. Night sweats, chills and fever were not infrequent. In one of our most recent patients, as well as in the one reported by Jamison and Hopkins, malaria was suspected and a diligent search made to rule it out. The fever charts of patients 1 and 2 are shown in figure 1. Intermittent fever, with temperature ranging from 99.8 to 101.2 F., was observed and persisted up to three or four weeks. In 3 patients no fever was noted. Tachycardia with a heart rate exceeding 100 per minute occurred in 4 patients. The respiratory rate varied from 20 to 80 and was over 25 in 7 patients during the episodes of fever and dyspnea. For 8 of the 11 patients the weight was recorded. In all of them loss of weight occurred, varying from 5 pounds (2.25 Kg.) in three weeks to 26 pounds (11.7 Kg.) in two months. It was frequently noted before other symptoms developed. Weakness over a long period was a characteristic finding. The blood pressure was not remarkably changed.

Examination of the chest revealed nothing striking. Impaired resonance and diminished breath sounds were noted in 4 instances, usually in the bases of the lungs posteriorly. In 8 patients rales were heard, chiefly in the bases. In 1 instance minimal signs of consolidation were heard in the base of the right lung an area in which lung puncture with biopsy was successful. The manifestations were bilateral in 6 instances.

Roentgen examination of the chest showed what was uniformly described as a miliary mottling throughout both lungs, most dense in the hilar areas. These areas in general had a ground glass appearance. In only 1 instance were the apexes involved. Examples of these changes and of their progress are presented in figures 2 and 3.

Bronchoscopy was carried out for 1 patient, and nothing worthy of note was observed. Bronchograms also failed to reveal anything significant. In Gillison and Taylor's patients bronchoscopy showed congestion of the trachea

Summary of Clinical Data on Cases Reported

Case No.	Age	Race	Length of Exposure (Weeks)	Cough	Dyspnea	Sputum	Hemoptysis	Night Sweats	Chills and Fever	Loss of Weight (Pounds)	Pharyngeal Irritation	Duration of Symptoms Before Admission (Weeks)	Cyanosis	Examination of Chest	Roentgenologic Picture of Chest	Days of Hospitalization	Follow-Up
1	18	W	4	+	+	+	+	0	0	28	0	1	0	Diminished breath and voice sounds over base of left lung, with limited expansion; no rales	Miliary ground glass mottling throughout both pulmonary fields, radiating from hili; apexes clear (fig. 2)	84	Chest roentgenologically clear (fig. 2) 1 month after discharge
2	46	W	3	+	+	+	0	+	+	10	0	1	0	Rales in bases of both lungs anteriorly and posteriorly	As above (fig. 3)	93	Chest roentgenologically clear 11 weeks after discharge
3	26	W	20	+	+	0	0	+	+	17	0	4	0	Impaired resonance and breath sounds in base of right lung; bilateral basal rales	As above	23	
4	30	N	6	+	+	+	0	—	—	..	+	3	0	Impaired resonance and diminished breath sounds in bases of both lungs posteriorly	As above	31	Chest roentgenologically clear 13 weeks after discharge
5	34	N	..	+	+	+	0	—	+	15	0	5	0	Impaired resonance upper lobe of right lung anteriorly; no rales	As above	9	Chest roentgenologically clear 13 weeks after discharge
6	19	W	28	+	+	+	0	—	—	20	0	12	0	Fine crackling rales at base of left lung posteriorly	As above	19	Chest roentgenologically slightly cleared on discharge; no follow-up
7	27	N	104	+	+	0	0	+	+	5	+	3	0	Fine rales in base of right lung posteriorly and in right axilla	As above	18	No follow-up
8	28	N	12	+	+	+	+	+	+	..	—	3	0	Rales in upper half of right side of chest; vocal fremitus increased	Apexes also involved	15	No follow-up
9	27	W	..	+	+	+	+	+	+	+ amt. ?	—	5	+	Diminished expansion at bases of both lungs; rales throughout both lungs, most marked in bases	Miliary ground glass mottling throughout both pulmonary fields, radiating from hili; apexes clear	86	Chest roentgenologically clear 2½ months after discharge
10	22	W	..	+	+	+	0	+	+	+ amt. ?	—	3	0	Fine rales bilaterally throughout pulmonary fields	As above	14	No follow-up
11	20	N	16	+	+	+	+	+	+	..	+	2	—	Diminished expansion at bases of both lungs; coarse rales at base of right lung posteriorly	As above	29	Chest roentgenologically clear 1 month after discharge

and bronchi and a white frothy sputum. These were noted in the late stages of the disease.

The sputum, already described as scanty and mucoid, persistently failed to reveal tubercle bacilli, even with concentration methods. In 4 cases repeated attempts were made to grow a fungus. On 1 occasion a positive culture for Monilia was obtained; in another patient a fungus was found but not identified. These organisms were considered as contaminants. The cellular content of the sputum consisted, in general, of polymorphonuclear leukocytes and lymphocytes. Eosinophils were not in evidence.

Studies of the blood were of interest. Leukocyte counts varied from 7,400 to 20,600. Ten of the 11 patients had counts above 10,000, averaging approximately 13,000. In 7 cases differential counts indicated polymorphonuclear leukocytosis, the percentage of polymorphonuclear cells varying from 73 to 90. Toxic granulations were in evidence, and there was a shift to the left. The proportion of eosinophils varied from 0.5 to 7 per cent, averaging 3.5 per cent. The numbers of mononuclears and of lymphocytes were in the normal range. In 5 cases Wintrobe sedimentation rates were 35 to 54 mm. per hour, a definite increase. In 4 instances the hematocrit reading was 46, and in 1 it was 48.5. The red blood cell counts on admission varied from 4,300,000 to 6,770,000 in 9 cases. The high value, of 6,770,000, occurred in the fifth week of the disease and was accompanied by a febrile reaction of 101 F. In cases 1 and 2 we noted the development of a polycythemia in the eighth and the twentieth week of the disease, respectively. This finding has not been recorded previously perhaps because of the lack of follow-up studies. The hemoglobin values were correspondingly elevated. Blood cultures and agglutination reactions for typhoid, paratyphoid, tularemia and undulant fever were negative in 3 cases. In cases 1 and 2 tests for psittacosis, carried out by Dr. Karl Meyer, of the Hooper Foundation, gave negative results. Routine urinalyses and determinations of blood chemistry were within normal variations.

A Mantoux test was done in 4 cases. In 2, the reaction was negative with dilutions of old tuberculin of 1:1,000 and 1:100. Cutaneous tests with bagasse extracts will be described later in the paper.

Treatment has consisted of rest in bed during the acute stages of the disease and palliative medication and procedures. In the 2 cases reported in detail a relationship between improvement and the administration of potassium iodide seemed to be evident. This change may have been coincidental.

The stay in the hospital varied from nine to ninety-three days and averaged thirty-eight and a third days. A follow-up investigation of 6 cases over periods of four months showed perfectly clear roentgenograms of the chest in 5 and a residual which appears at present to be clearing in 1.

Jamison and Hopkins called the condition "bagasscosis"; according to Castleden and Hamilton-Paterson the term "bagassosis" is better. Since the suffix "osis" is properly added only to words formed from Greek roots [2] and since we have as yet not been able to trace the term "bagasse" to the Greek, we prefer the simple term "bagasse disease of the lungs."

The cause of the clinical picture has been undetermined. The lack of autopsy material has handicapped the search for the cause. We have been fortunate in obtaining sections of a lung of 1 patient at autopsy and of another by lung puncture.[3] The observations on these sections will be discussed. Experimental production of the disease has thus far failed. A relationship between the development of the picture and work in bagasse dust seems clear. This association was noted by Jamison and Hopkins [1a] as well as by others.[1b, c] Although bagasse dust up to the present time has not been shown conclusively to be the cause of the symptoms, the close relationship between the patients' work and the characteristic clinical picture, together with the absence of the disease in other persons, so far as observers have noted, points clearly to a cause and effect relationship between exposure to bagasse dust and the development of symptoms. As will be discussed later, we have identified bagasse dust in sections of lungs.

In their report Jamison and Hopkins suggested a fungus as the cause. They isolated a fungus but did not state its characteristics or type. In one instance we found Monilia in the sputum but considered that it was probably a contaminant, as is often the case. Castleden and Hamilton-Paterson attempted without success to isolate a fungus. Gillison and Taylor had the same experience. The roentgenograms of the chest remind one somewhat of the maple bark disease,[4] a fungus infection, but we have been unable to

2. Garber, S. T.: Stedman's Practical Medical Dictionary, ed. 15, Baltimore, Williams & Wilkins Company, 1942.

3. Sodeman, W. A., and Pullen, R. L.: Bagasse Disease of the Lungs, New Orleans M. & S. J. **95**:558-560 (June) 1943.

4. Towey, J. W.; Sweany, H. C., and Huron, W. H.: Severe Bronchial Asthma Apparently Due to Fungus Spores Found in Maple Bark, J. A. M. A. **99**:453-459 (Aug. 6) 1932.

isolate the causative organism or any other organism which would produce a similar picture. Investigation of the bagasse itself is difficult. After lying in the field for variable lengths of time with fermentation and fungous and bacterial invasion taking place in the bales, bagasse is a complex mixture not easy to analyze. One might mention, however, that workers exposed to dust of the insulation board after processing, which includes heat treatment, have not as yet been reported to acquire bagasse disease. Processing destroys not only fungi and bacteria but allergenic protein as well. The fungus theory has at present little supporting evidence, but an infectious theory cannot be disproved on negative or indirect grounds.

Some relationship to byssinosis, the syndrome occurring among persons working with low grade stained cotton, might be suspected. This syndrome is an acute illness that develops in workers exposed to high concentrations of dust, particularly in rural mattress making centers, cotton mills and upholstering plants,[5] and is thought to be caused by inhalation of substances produced by certain gram-negative bacteria in or on the dust. However, the clinical picture is distinctly different from that of bagasse disease. The onset is sudden, within a few hours after exposure. Dry throat, aches, fatigue, headache, cough, chills, fever, and nausea and vomiting occur. Conjunctival irritation is present. The symptoms in the acute phase last only one to two days.

Castleden and Hamilton-Paterson [1b] suggested an allergic reaction as the cause of bagasse disease. They based this suggestion on the positive results of cutaneous tests. Realizing the possibility that an allergic factor could be responsible for the disease, they prepared extracts for the tests in four menstruums: tenth-normal solution of sodium hydroxide, tenth-normal hydrochloric acid, isotonic solution of sodium chloride and 30 per cent alcohol in distilled water. Tricresol, 0.25 per cent, was added to each. The extracts containing acid and alkali were neutralized before use. In their case 2, extracts 1, 2 and 4, given intracutaneously in doses of 0.2 cc., all elicited a wheal maximal in thirty minutes and a flare maximal in thirty-six hours. Controls of the menstruum were also prepared. The saline extract gave a flare but no wheal. Three patients tested gave positive reactions, and a group of controls who did not have bagasse disease was reported as having negative reactions. It appears that these were tested solely with the saline extract, the one which in their case 2 caused a flare only, without a wheal.

From these results Castleden and Hamilton-Paterson concluded that whole bagasse contains an antigen soluble in isotonic solution of sodium chloride to which workers inhaling the dust can be sensitized. They suggested that the acute phase of the disease is possibly an allergic response to this antigen, with, or probably without, an infective element.

We repeated these tests on our patients. Through the efforts of Dr. S. S. Pinto, chief of the section of industrial hygiene of the Louisiana State Department of Health, we were able to obtain a sample of bagasse from a bale bound for England. Dr. Vincent Derbes, allergist to the Hutchinson Memorial Clinic, made up extracts of this material according to the directions of Castleden and Hamilton-Paterson. With all four extracts we tested 3 patients, 2 after recovery from the disease and 1 during the sixth week of the disease. In addition, 5 controls, 3 who had no knowledge of ever contacting bagasse, 1 who in his youth had cut cane for several weeks and another who had worked as watchman in an area where bales of bagasse were stored, were tested. The doses of the English observers, as well as 0.04 cc. doses, were used intracutaneously. The developing reactions in 5 of these subjects were traced at the end of thirty minutes, with the results shown in figure 4. Positive results were obtained in each instance, which led us to the conclusion that the reactions were irritation phenomena, perhaps with release of histamine, and did not necessarily indicate sensitization to bagasse. At each site, particularly with the sodium hydroxide and the saline extract, extensive areas of reaction twice or more the size of the immediate flare were seen at twenty-four to thirty-six hours. This reaction was not the flare of Lewis' triple response but a diffuse redness of the type seen in the positive reactions to the tuberculin test and similar tests. Of its interpretation we are in doubt, but, as is well known, the response cannot be construed to indicate an allergy to the extract used. We encountered no absolutely negative reactions to tests, as did Castleden and Hamilton-Paterson. Dr. Derbes concurred in these interpretations.

Allergic pulmonary disease is well known. The syndrome described by Loeffler appears to be such. It is a transient pulmonary infiltration accompanied by eosinophilia in the blood, and, as in the present series of patients, eventuates in the spontaneous disappearance of symptoms

5. Schneiter, R.; Neal, P. A., and Caminita, B. H.: Etiology of Acute Illness Among Workers Using Low-Grade Stained Cotton, Am. J. Pub. Health **32**:1345-1359 (Dec.) 1942.

and signs.[6] The course of the disease is, however, distinctly different. Symptoms include attacks of asthma with cough, fever, leukocytosis, eosinophilia and elevated sedimentation rate. Only a few rales are heard over the involved pulmonary areas. Roentgen findings differ considerably, with areas of consolidation appearing and disappearing rapidly, and the picture clears up in about a week, with only a few fine scars left in the lung.

Tuberculosis is to be suspected as the cause of the condition, especially from the roentgen appearance of the lungs. The clinical associations, the absence of tubercle bacilli in the sputum when it is examined by concentration methods, the results of the tuberculin test and the course of the disease, together with observations made at

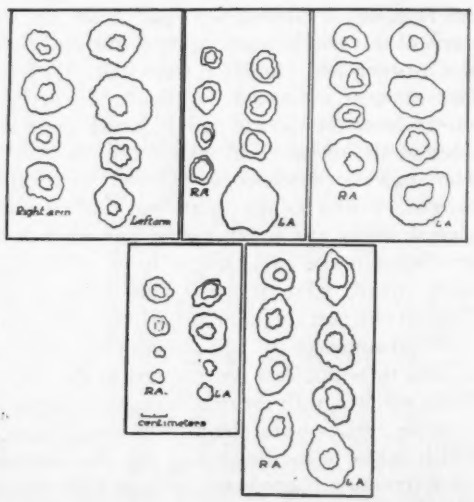

Fig. 4.—Tracings taken at the end of thirty minutes of the cutaneous responses to intracutaneous injection of extracts of bagasse in 5 subjects. The central area in each instance represents the wheal and the large area the extent of the flare. In each arm the reactions from above downward represent the response to bagasse extracted in (1) 30 per cent alcohol, (2) tenth-normal sodium hydroxide solution, (3) tenth-normal hydrochloric acid, and (4) isotonic solution of sodium chloride (see text). Reactions in the right arm in each instance represent the response to 0.04 cc. of extract; in the left arm, to 0.2 cc. The responses shown in the last diagram were found in the sixth week of the disease (case 3). The remaining responses are from the control series.

biopsy and at autopsy, rule it out rather conclusively. On similar grounds Boeck's sarcoid is eliminated.

Finally to be considered as a possible cause of the clinical picture is pneumonoconiosis. This general term covers all diseases due to dust, whether fibrous or nonfibrous.[7] While bagasse is described as containing 5 to 7 per cent silica (silicon dioxide), the short incubation period of the disease and its short course, with complete clearing of the lungs from the clinical and roentgenologic standpoints, speak distinctly against the possibility that the picture is a phase or type of silicosis, even of the acute variety. Castleden and Paterson's patient with residual lesions had worked as a coal miner for twenty years.[1b]

Exposure to a variety of organic and inorganic dusts other than those active from their silica content may produce symptoms. Bronchitis is not uncommon, and its cause often goes unrecognized. Particles sufficiently small may reach the alveoli and set up a pneumonitis. Our patients showed roentgen evidence, leukocytosis, variable degrees of fever and raising of sputum, all of which are compatible with a diagnosis of pneumonitis. The usual types of pneumonia, including atypical or virus pneumonia, are so different in all respects from this syndrome that they seem out of the picture. But a pneumonitis from dust is likely, and the examination of tissue obtained by lung puncture from a patient in the sixth and seventh weeks of the disease supports the view that bagasse particles mechanically, chemically, through one of its fractions or by introduction of an unknown infection, are responsible for the pathologic picture. Sections of these specimens obtained from involved areas are reproduced in figure 5. A section from the first biopsy specimen and one obtained at an autopsy in a case of bagasse disease have previously been published.[3] In that report the first biopsy was described as showing pulmonary tissue with several "spicules" of an irregular foreign material embedded in it. The foreign bodies were similar microscopically to bagasse. Under the polarizing microscope these "spicules" were seen to rotate polarized light. This examination brought out many smaller scattered pieces, with an average diameter of 2 to 8 microns. These structures were seen especially in the fibroblastic reaction of the interstitial tissue of the lung. Dr. B. Pearson of the department of pathology, who reviewed all these sections, described the second biopsy specimen, taken a week later, as follows:

> The specimen showed a reaction similar to the first, but there were only a few "spicules" and these were of the smaller variety previously described. They were present in areas in which there was an increase in fibrous tissue and reacted as bagasse fibers characteristically do to polarized light. An additional feature

6. Hoff, A., and Hicks, H. M.: Transient Pulmonary Infiltrations, Am. Rev. Tuberc. **45**:194-199 (Feb.) 1942.

7. Harrington, D., and Davenport, S. J.: Review of Literature on Effects of Breathing Dusts with Special Reference to Silicosis, Bulletin 400, United States Department of the Interior, Bureau of Mines, 1937.

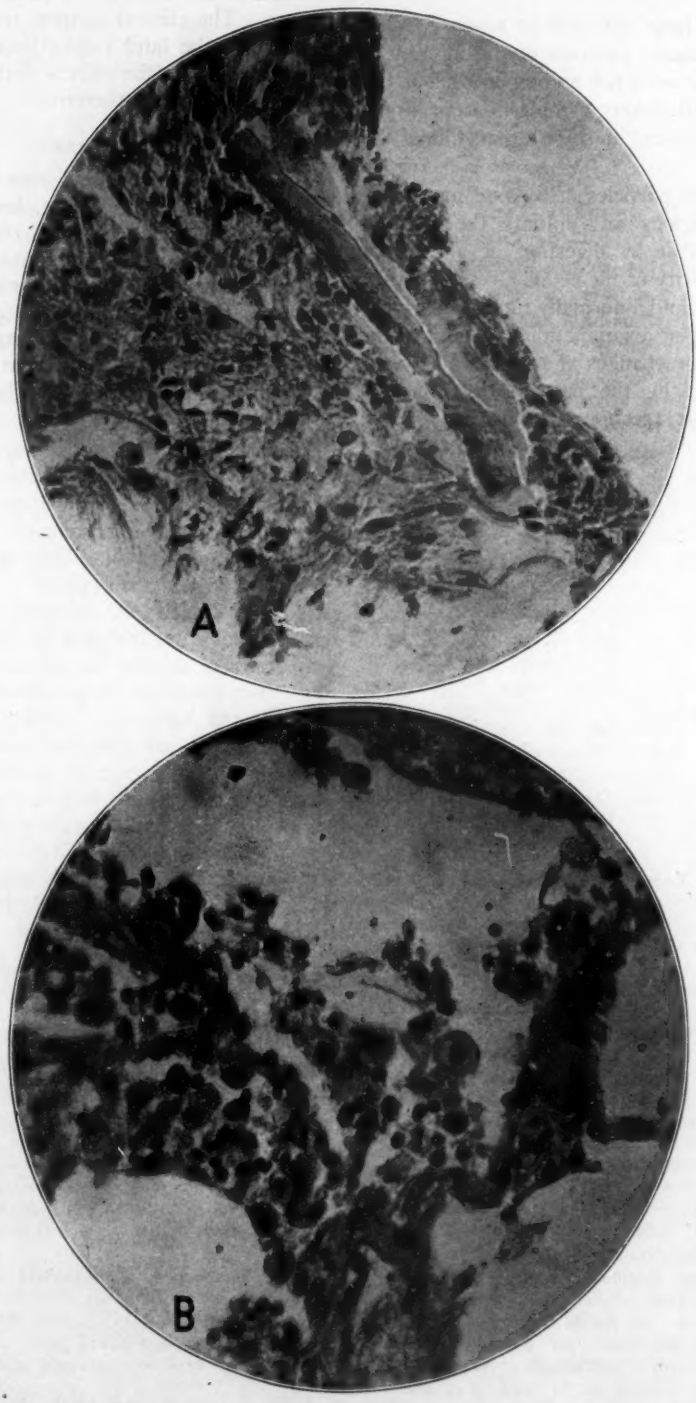

Fig. 5.—Sections of needle biopsy specimens of the lung obtained from patient 3 in the sixth (*A*) and seventh (*B*) weeks of the disease.

was the many large cells with a foamy cytoplasm in the alveolar spaces.

The section of lung obtained at autopsy [8] also showed a fibroblastic reaction of the interstitial tissue. Spicules were not as numerous, but the alveolar cells with foamy cytoplasm were larger and more numerous, in some areas filling the alveolar spaces.

It appears that particles of bagasse may enter the alveolar regions and initiate the reaction described and that by digestion or absorption through the activity of the cellular response they may be removed and a normally functioning lung, clear on roentgen examination, remain. The mechanism of the changes and the nature of the stimulus set up by the bagasse dust to produce the cellular reaction are obscure. These are the first demonstrations we have seen of this reaction in the tissues of a patient with bagasse disease. The clinical picture, from the striking dyspnea to the later polycythemia, may be explained as due to the effects of this reaction and the anoxia resultant therefrom.

SUMMARY

Eleven cases of bagasse disease of the lung have been added to the literature, bringing the total number of reported cases to 18. Observations of the group disclose a number of constant features which produce a characteristic clinical picture. Evidence from histologic study of involved areas of the lung indicates the presence of bagasse dust with a severe and unusual cellular reaction, the nature of which has not yet been established.

DIFFUSE ISOLATED MYOCARDITIS ASSOCIATED WITH DIETARY DEFICIENCY

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In recent years there have appeared in the literature many reports describing unusual cases of myocarditis of unknown cause. Various appelations have been applied to the myocardial disease: Fiedler's myocarditis, diffuse isolated myocarditis, myocarditis perniciosa, diffuse granulomatous myocarditis and others. The condition is usually attributed to such causes as infections of the upper respiratory tract, influenza, burns, toxemias and injuries produced by various chemicals. Magner [1] expressed the opinion that obscurity of cause could not be considered as justification for the grouping together of these conditions as manifestations of a single disease. It appeared to him that the group is a heterogenous one, possibly including atypical varieties of tuberculous, syphilitic and rheumatic myocarditis as well as certain other inflammatory conditions of unknown and probably variable causation. However, Saphir,[2] who recently published an extensive review of the literature pertaining to myocarditis, stated the belief that "one is justified in accepting the occurrence of isolated myocarditis in the sense of a more or less diffuse inflammatory lesion if every known cause for this type of myocarditis is ruled out and if the myocarditis is found in the absence of any major pathologic condition involving either the endocardium and pericardium or the entire body." Lindberg [3] compared the myocardial lesions of his patient with the serous myocarditis described by Wenckebach [4] and others and suggested that isolated myocarditis might represent the end stage of beriberi. More recently, Smith and Furth [5] reported 3 cases of fibrosis of the endocardium and myocardium with mural thrombosis. In these cases the changes were not attributable to arteriosclerosis, hypertension or valvular disease. There was abundant evidence of dietary deficiency, and the question was raised whether these changes could represent a variant of beriberi heart. The case presented here resembles pathologically those of Smith and Furth. The disease was associated with a prolonged history of malnutrition, and there is evidence indicating that dietary deficiency of vitamin B may have been an important etiologic factor. The case, therefore, seems worthy of record.

REPORT OF A CASE

I. M., a 15 year old white girl, was admitted to the Royal Victoria Hospital, Montreal, on April 10, 1943, in a state of severe cardiac insufficiency. The family history was barren of relevant data. At birth the patient appeared normal in every way. In infancy she suffered from a "weeping eczema," which disappeared completely at the age of 3 years. At 5 she began to have a hacking productive cough which was severe in winter but mild in summer; thereafter, pharyngitis was frequently experienced, gain in weight was retarded and loss of color and of strength was progressive. At 7 she was admitted to the Montreal General Hospital, suffering from malnutrition and chronic tonsillitis. Heavy peribronchial shadows seen on roentgen examination suggested bronchiectasis, but this diagnosis was not further substantiated, and after two months of beneficial dietary and general supportive therapy she was discharged to a convalescent home in a much improved condition. In October 1942, at the age of 14 years, she was again admitted to the same hospital, complaining of cough. She was a poorly developed and malnourished girl who weighed approximately 35 pounds (15.9 Kg.) less than average for her age and height. Roentgen examination of the chest revealed hilar and bronchovascular markings. An occasional extrasystole was detected, and the second heart sound was loud throughout the precordium; the blood pressure was 100 systolic and 60 diastolic. The electrocardiogram demonstrated an irregularity of sinus origin. In the first lead the Q R S complex was notched in the upstroke. There were a slight delay in the conduction time and a suggestion of left axis deviation. An electrocardiogram made one week after the first showed the same delay in conduction. These findings were interpreted as evidence of an unstable cardiac conducting mechanism. The hemogram demonstrated a mild anemia of secondary type. During the seven week period of hospitalization there was no fever, and with rest in bed, high caloric diet, high vitamin intake and

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1. Magner, D.: A Case of Fatal Subacute Myocarditis of Unknown Etiology, Am. J. M. Sc. **198**: 246, 1939.

2. Saphir, O.: Myocarditis: A General Review, with an Analysis of Two Hundred and Forty Cases, Arch. Path. **32**:1000 (Dec.) 1941; **33**:88 (Jan.) 1942.

3. Lindberg, K.: Zur Frage von den sogenannten isolierten chronischen Myokarditen, Acta med. Scandinav. **95**:281, 1938.

4. Wenckebach, K. F., cited by Saphir.[2]

5. Smith, J. J., and Furth, J.: Fibrosis of Endocardium and Myocardium with Mural Thrombosis, Arch. Int. Med. **71**:602 (May) 1943.

ultraviolet therapy improvement was striking. She had gained 12 pounds (5.4 Kg.) (about a 20 per cent increase over the body weight on admission) when she was discharged, in December 1942.

The patient then returned home to continue as nearly as possible the hospital regimen which had been so beneficial. She resumed full activity and returned to school in January 1943. Her health remained fairly good until March, when she became increasingly restless, had frequent headaches, gradually lost weight and color and began to vomit occasionally. She experienced mild precordial pain and had dyspnea on slight exertion. Once or twice she coughed up bloody sputum, and on the day of readmission to the hospital she had a slight nosebleed.

On her final admission to the hospital, physical examination revealed no fever; the pulse rate was 108 and the respiratory rate 28 per minute. The patient was restless, dyspneic and pallid. There was pediculosis capitis. The pulse was soft, rapid and regular, and the blood pressure was 92 systolic and 70 diastolic. The heart was enlarged, the point of maximum impulse

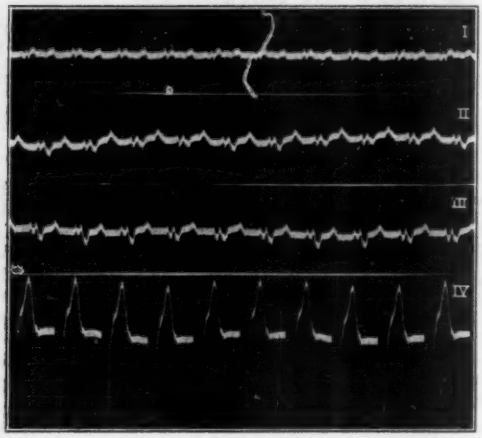

Fig. 1.—Electrocardiogram made on April 12, 1943, four days before death, showing abnormalities detailed in the text.

being palpable 2 cm. beyond the left nipple line. In the apical and pulmonic areas the first heart sound was reduplicated but valvular murmurs were not heard. Both lungs were dull to percussion at the bases, and fluid was detected in the abdomen. The margin of the liver was felt at the level of the umbilicus, and there was tenderness to palpation in the right upper quadrant of the abdomen. The spleen and other viscera were impalpable. Pitting edema extended from both lower extremities over the vulva and the sacral area.

The urine contained a trace of albumin. The hemogram was normal. Intradermal tuberculin tests and Kahn tests of the blood elicited negative reactions. Aerobic and anaerobic cultures of blood yielded no growth. Roentgenography revealed cardiac enlargement toward the left; the right margin of the heart was indistinct because of increased radiopacity in the lower right pulmonary field. Throughout the upper part of the right and the entire left pulmonary field there was a notable increase in detail. The electrocardiogram showed regular rhythm, a ventricular rate of 90 per minute, auriculoventricular conduction time of twenty-four to twenty-six hundredths second, left preponderance, low QRS voltage, split QRS complex and intraventricular time of sixteen-hundredths second. In lead I the T wave was diphasic; in lead IV there were high T voltage and elevation of the ST interval (fig. 1).

The clinical diagnosis was congestive heart failure, but the nature of the underlying cause was not apparent. She was given digitalis, restricted fluids and a salt-free diet. Thiamine hydrochloride was injected intramuscularly in doses of 100 mg., and vitamins B and C were given by mouth. The rapid pulse and respiratory rates continued, and she remained afebrile. Occasionally she coughed blood-tinged sputum, and frequent use was made of the oxygen tent. On April 15 she became cyanotic, her breathing was labored and she complained of severe abdominal pain. Death occurred, somewhat unexpectedly, on April 16. An electrocardiogram made during the last minutes of life showed complete heart block (rate 15 per minute) and left bundle branch lesion terminating in ventricular fibrillation just before death.

Postmortem Examination.—Autopsy two and one-half hours after death included examination of the thoracic and abdominal organs and the brain. The noteworthy conditions observed were the following:

Gross Examination: The body, which measured 153 cm. in length, was that of a poorly nourished girl showing early pubertal changes. The scleras and the skin were pale, and the lips and the oral mucosa were cyanotic. Greatly distended superficial veins were prominent in the neck. The rounded, moderately protuberant abdominal wall was covered by a thin layer of subcutaneous fat, and numerous striae had formed in the overlying skin. Pitting edema involved both lower extremities, the vulva and the sacral area. The tips of the fingers and toes were cyanotic but were not clubbed. Within the thorax, the heart and pericardial sac occupied the greater portion of the transverse diameter. The pericardial sac contained 75 cc. of clear yellow fluid; the serous surfaces were free from lesions. The pulmonary artery, opened in situ, contained only an elongated mass of postmortem clot.

The heart (figs. 2, 3 and 4) weighed 295 Gm. The pericardial membrane was everywhere thin and smooth. All the chambers were moderately dilated, and the pulmonary conus was distinctly larger than the aortic conus. Both ventricular walls were hypertrophied; the right measured 6 mm. in thickness, and the left, 10 mm. at the thickest portions. The myocardium had a variegated reddish brown to grayish brown mottled appearance, and its consistency was soft. However, several small irregular gray areas of firm consistency were noticeable on the cut edges of both ventricles. Near the endocardium the myocardium was much grayer and firmer than elsewhere. The trabeculae carneae and the papillary muscles were broad and flat; the pectinate muscles were unusually prominent. At a site a few centimeters from the aortic ring opposite the anterior margin of the interventricular septum the myocardium of the left ventricle showed a reddish brown area in the superficial half of its thickness. The circumferences of the valves were within normal limits; the leaflets and cusps appeared entirely normal. The mural endocardium of the right atrium was moderately thickened in a diffuse manner, and some small irregular gray patches of slight thickening were visible in the endocardium of the right ventricle overlying the interventricular septum. Greater and more extensive fibrous thickening was present diffusely throughout the endocardial lining of the left auricle and in wide areas of the mural endocardium of the left ventricle, especially over the interventricular septum and the anterior wall of the ventricle. Small gray firmly adherent mural

Fig. 2.—Photograph showing the right side of the heart and the tricuspid valve. The pericardium and tricuspid valve are normal. The chambers are dilated and the walls hypertrophied. The cut edge of the myocardium is mottled with irregular gray areas of fibrous scarring. The endocardium of the auricle shows uniform gray fibrous thickening, while that of the ventricle shows patchy thickening over the interventricular septum. Several small mural thrombi are visible between the pectinate muscles of the auricle, and a large thrombus mass is present at the apex of the right ventricle.

Fig. 3.—Photograph showing the left side of the heart and the mitral valve, which is normal. The endocardium of the auricle is uniformly thickened, while that of the ventricle shows similar thickening most pronounced over the flat atrophied trabeculae corneae of the anterolateral ventricular wall. Both chambers are dilated and hypertrophied. The cut edge of the ventricle is mottled with gray areas of fibrous scar tissue most prominent just beneath the endocardium.

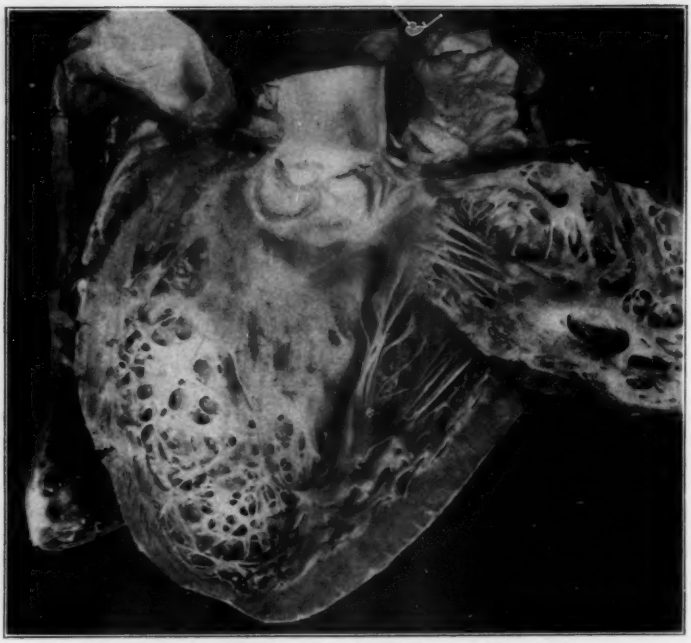

Fig. 4.—Photograph showing the dilated and hypertrophied left ventricle with mottling of its cut edges by fibrous scar tissue. The mitral and aortic valves are normal, but the ventricular endocardium is thick and gray, especially over the septum and anterolateral wall of the ventricle. Several mural thrombi are visible between trabeculae carneae near the aortic conus and near the apex.

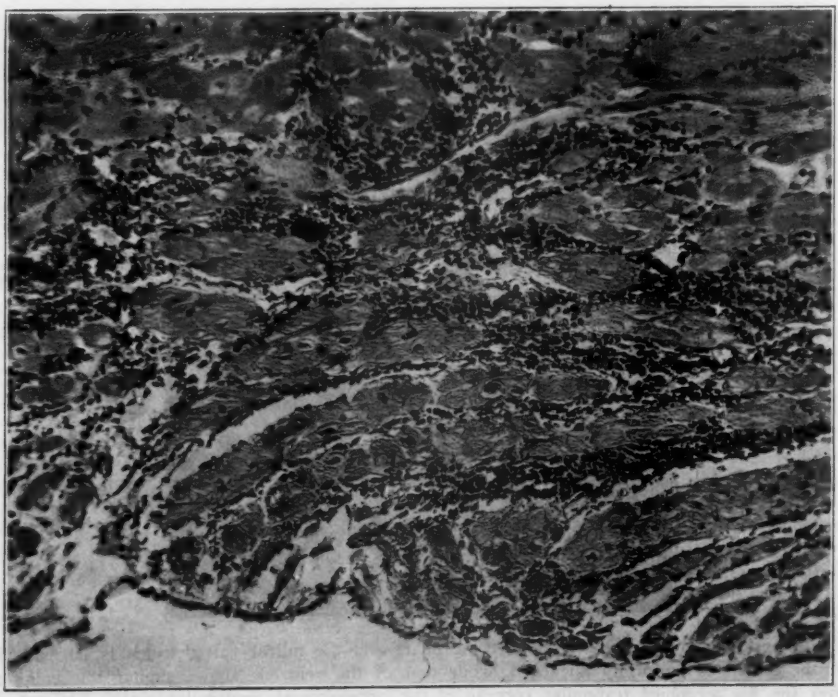

Fig. 5.—Photomicrograph at low magnification of an area of acute myocarditis. The infiltration of inflammatory cells extends between the swollen granular muscle fibers. In this field the endocardium is only slightly affected.

thrombi were found between the pectinate muscles of the right auricle, in the tip of the left auricular appendage and between the trabeculae carneae of both ventricles. The coronary arteries were regular in diameter and perfectly patent. The aorta showed fatty streaks in the abdominal portion. Except for distention of veins throughout the systemic and portal systems, no abnormalities of the blood vessels were detected.

The right and left pleural spaces contained 700 and 250 cc. respectively of slightly cloudy yellow fluid. The right lung weighed 370 Gm. and the left 225 Gm. The external surfaces and the cut surfaces were dark bluish red, and the consistency of the parenchyma was firmer than usual in all areas. The middle lobe of the right lung and the lower lobe of both lungs were almost hard, and each presented several large wedgelike dark red areas which tended to bulge slightly on the external surfaces. No occlusive lesions were found in any pulmonary vessel. The bronchial mucosa, although smooth and glistening, was rather red. The peritoneal cavity contained 1,000 cc. of slightly turbid yellow fluid. The liver extended several fingerbreadths below the costal margin, weighed 900 Gm. and had the characteristics of "nutmeg liver" to a marked degree. The spleen weighed 100 Gm.; it was dark blue, exuded only a little dark red blood and retained its shape when sectioned. The right kidney weighed 90 Gm. and the left 80 Gm. Their capsules stripped readily, perfectly smooth surfaces being left. Section revealed hyperemia accentuating the corticomedullary boundaries. Both ovaries showed small irregular dark red areas on the surfaces. No abnormalities were noted in any other organ.

Microscopic Examination: Many sections were taken from the walls of all the chambers of the heart; these were stained with hematoxylin and eosin and various special stains (including Mallory's stain for connective tissue, Verhoeff's stain for elastic tissue, sudan III, Glynn's stain for bacteria and Custer's stain for granules). No section was free from lesions, although the appearance varied greatly in different sections and in different fields of any single section. The simplest lesions were widespread irregular areas of hydropic degeneration of heart muscle fibers. In cross sections the endomysial sheath was distended and contained a large clear space, at the center of which a swollen, pale, rounded nucleus or a shrunken, angular, pyknotic one was often seen. In less degenerate fibers the myofibrils were clumped together so as to give a coarsely granular appearance. Tangential and longitudinal sections of muscle fibers showed cross striations even when severely affected. Another variety of lesion (figs. 5 and 6) consisted of small focal areas of acute inflammation characterized by pronounced exudation of neutrophilic polymorphonuclear cells and red corpuscles; in these areas edema and hyperemia were severe, and the muscle fibers stained with variable intensity, some appearing necrotic. Eosinophilic leukocytes were rarely encountered, and lymphocytes, macrophages and multinucleated giant cells were entirely absent. Special stains

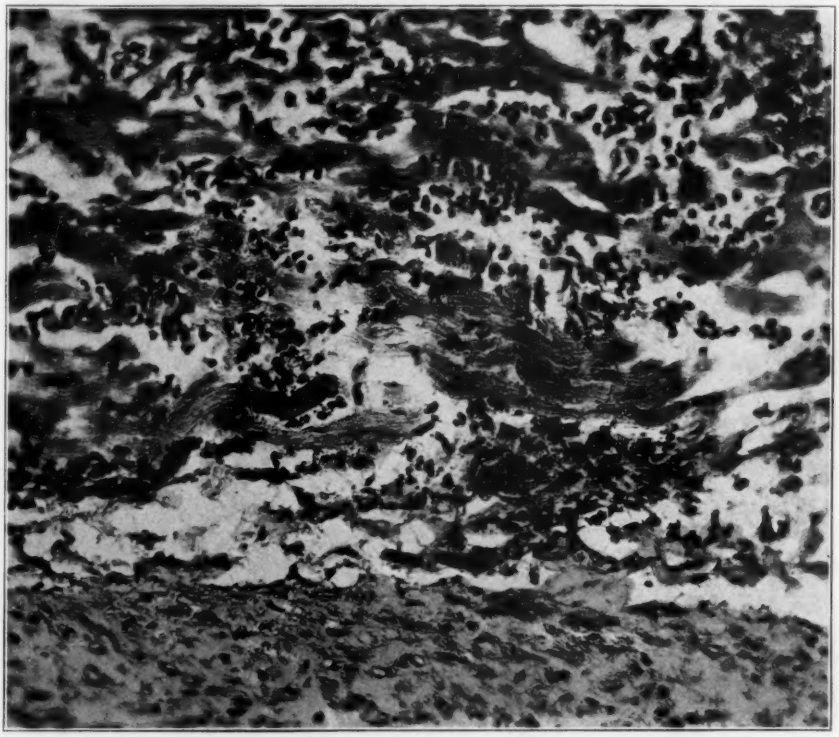

Fig. 6.—Photomicrograph at high magnification of an area of acute myocarditis, showing degenerative and early necrotic changes in the muscle fibers and an interstitial infiltration of polymorphonuclear leukocytes and red blood cells. There is striking proliferation of fibrous tissue in the adjacent endocardium (below).

for bacteria failed to reveal any organisms in these areas on careful search. Almost every section contained one or more irregular areas wherein myocardial fibers were replaced by rather dense collagenous tissue. Occasionally an engorged capillary associated with small groups of neutrophilic leukocytes, lymphocytes and rare macrophages was encountered in these areas (fig. 7); usually, however, the scars were strikingly acellular (fig. 8). Often a few bundles of myocardial fibers were present in the midst of such a chronic lesion; of the individual fibers, some were noticeably hypertrophic while others were equally atrophic. The nuclei of the hypertrophic fibers were enormous; but neither were multinucleated cells found in any of these lesions, nor was there any necrosis. The areas of most abundant proliferation. However, there was no significant degree of narrowing of the lumens.

Microscopic sections of the lungs showed chronic passive hyperemia with extremely large numbers of red cells and masses of amorphous eosinophilic granular material filling the alveoli of many lobules. Large macrophages were numerous in the alveolar spaces and in the bronchovascular supporting tissues; many contained brown granular pigment, and others were strikingly vacuolated. Perles' reaction was strongly positive for hemosiderin, and sudan III showed the vacuolation to be caused by fat globules. In such areas there was a tendency for fibroblasts to grow into the intra-alveolar masses. The bronchioles showed a mild chronic inflammation, with thick basement membranes. There was

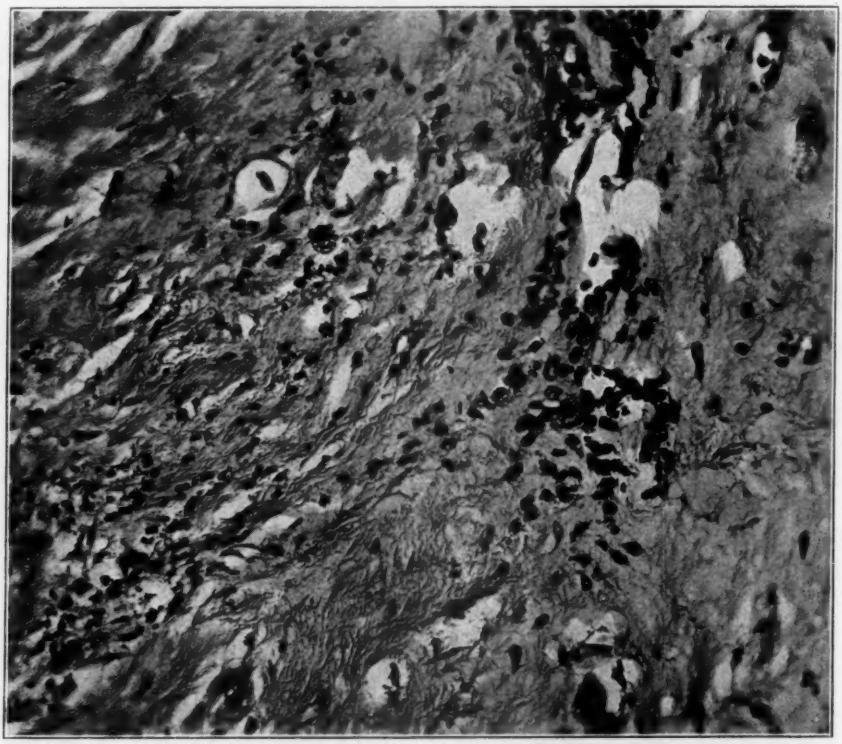

Fig. 7.—Photomicrograph at high magnification of a subacute inflammatory lesion in the myocardium. The inflammatory infiltration is composed of polymorphonuclear leukocytes and lymphocytes. Multinucleated giant cells are lacking. There is replacement by fibrous scar tissue of all but a few degenerate and atrophied myocardial fibers.

scarring were situated in the inner third of the myocardium and frequently involved the endocardium also. In every instance, however, such endocardial lesions, whether of acute or of chronic character, were related to underlying myocardial ones. By no means all of the endomyocardial lesions were associated with mural thrombosis; such thrombi as were found grossly were well organized at their points of attachment. Masses of granular calcium had been precipitated within the structure of the largest thrombus (near the apex of the right ventricle). Sections of the valves demonstrated their integrity. In all sections small branches of the coronary arteries were intact and patent; in larger branches and in both main coronary arteries the intima showed an unusual degree of loose cellular no evidence of occlusion of pulmonary vessels. The liver showed severe chronic passive hyperemia and contained several small necroses surrounded by an exudate composed of polymorphonuclear leukocytes. The spleen and pancreas showed chronic passive congestion; the adrenal glands were hyperemic. Pronounced cloudy swelling and hyperemia were the only alterations of the kidneys. No significant lesions were seen in the sections of any other organs, including those of the brain.

Pathologic Diagnosis: The diagnoses were: diffuse isolated myocarditis; diffuse fibrosis of the myocardium; hypertrophy and dilatation of the heart; mural thrombi of the heart (all chambers); chronic passive hyperemia of the lungs, liver, pancreas and spleen; anasarca;

ascites; bilateral hydrothorax; malnutrition; chronic bronchitis; slight lipid pneumonia; fatty streaks of the aorta; pediculosis capitis.

COMMENT

The widespread myocardial lesions which have been described were undoubtedly responsible for the death of this patient from heart block and ventricular fibrillation. Although mural thrombi were present in all chambers of the heart, no evidence of pulmonic or systemic embolization was discovered. The mild chronic bronchitis and slight lipid pneumonia could scarcely have been responsible in any immediate way for death. All other pathologic conditions were consistent with chronic progressive myocardial insufficiency.

The unusual character of the myocarditis is obvious. None of the usual causes of myocarditis could be detected from the clinical or pathologic studies. The patient had never had any of the common infectious diseases of childhood. Neither the clinical nor the pathologic studies revealed conditions suggestive of rheumatic heart disease. Although there was extensive mural endocardial involvement in areas overlying myocardial lesions, there was no evidence of valvular endocarditis. Cultures of blood and staining of sections of the heart for bacteria did not reveal their presence, and there were no metastatic pyemic lesions in any organ. The patient's response to intradermal injection of tuberculin was negative, and there was no pathologic lesion suggestive of tuberculosis anywhere. The Kahn reaction of the blood was negative, and there was no clinical or pathologic evidence of congenital or acquired syphilis. Moreover, the myocardial lesions were not granulomatous. Viral, protozoal and helminthic agents could not be even inferentially incriminated. Thyroid disease, uremia, poisoning with various chemicals, burns and serum sickness are occasionally accompanied by slight inconstant and variable alterations in the myocardium, but none of these conditions had ever been experienced by this patient. Periarteritis nodosa may be excluded because of the absence of inflamed or appreciably narrowed blood vessels from all the tissues examined. No sulfonamide compounds were ever given to this patient so far as could be determined; hence the possibility that the lesions represent an extraordinary example of the interstitial myocarditis described by

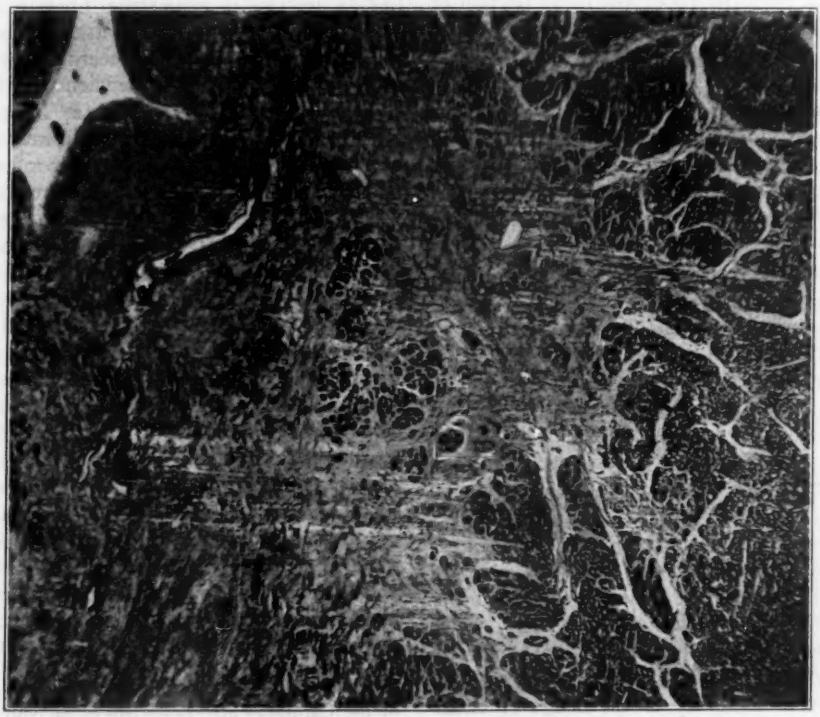

Fig. 8.—Photomicrograph at low magnification of a large irregular area of scarring in the inner third of the myocardium. Inflammatory cells are extremely few. Some of the remaining muscle fibers enclosed in scar tissue show hypertrophy; others are atrophied.

French and Weller [6] following the use of sulfonamide compounds is, at best, remote. Furthermore, the paucity of eosinophilic polymorphonuclear leukocytes in the more acute lesions and the advanced chronicity of many lesions constitute a dissimilarity to the myocarditis described by them. Disseminated lupus erythematosus may involve the heart muscle as well as the endocardium, but the dermal and systemic features of that disease were lacking in this instance. Thus, all known causes of myocarditis having been excluded and the absence of any major pathologic condition involving the endocardium, the pericardium or any other portion of the body having been determined, the myocardial disease described may be classified as diffuse isolated myocarditis.

As one considers the possible etiologic factors in this case, three outstanding features are notable: the weeping eczema during infancy, the presence of chronic tonsillitis and bronchitis with slight lipid pneumonia and the prolonged period of malnutrition.

The first deserves mention because the literature contains several reports of isolated myocarditis occurring in patients who were being treated with arsenical drugs for syphilitic dermatitis and with sulfur preparations for exfoliative dermatitis at the time of death. In the present instance nothing is known of the eczema except that after three years it disappeared entirely, leaving the patient in apparently unaltered good health.

The second feature is reminiscent of Franz's case [7] of an elderly woman who had received injections of epinephrine hydrochloride for bronchial asthma over a period of many years. Such cases caused Saphir [2] to remark that the common etiologic factor suggested by them is a peculiar hypersensitivity to the drugs or chemicals used in treatment. The respiratory conditions of the present patient, however, were never so treated; hence, they would seem to have played no more than an incidental role.

The third feature, malnutrition, has not often been reported. The cases of Lindberg [3] and of Smith and Furth [5] have been mentioned. Most accounts of beriberi heart describe dilatation of the right chambers of the heart, especially of the pulmonary conus, and microscopic changes which, according to Weiss and Wilkins,[8] are neither constant nor characteristic. Recent reports of experimental thiamine deficiency give rather confusing observations. Follis, Miller and Wintrobe [9] found cardiac dilatation without hypertrophy and focal and diffuse myocardial necrosis in pigs dying of thiamine deficiency; in animals which had passed through several episodes of severe thiamine deficiency, scars marking healed necrotic lesions were found. The similarity of the lesions to those in some cases of Fiedler's myocarditis was pointed out. By utilizing a diet adequate in all known respects except for an extremely low content of potassium, Follis, Orent-Keiles and McCollum [10] produced in rats necrosis of myocardial fibers followed by scarring. Later, Follis [11] was able to prevent the development of such necroses by feeding diets which were also deficient in thiamine. Thomas, Mylon and Winternitz [12] studied vitamin B and potassium deficiency in rats and hogs. They found myocardial lesions characterized by necrosis of muscle fibers and pronounced cellular infiltration; no evidence emphasized one or other factor as primarily requisite for cardiac injury. Further investigation showed that deficiency of vitamin B_6 when coupled with deficiency of potassium produced cardiac damage in rats but that deficiencies in either thiamine or riboflavin together with potassium deficiency produced no significant changes. It is noteworthy that Follis and co-workers [9] found no pathologic changes in the hearts of pigs killed at a time when no clinical or chemical evidence of thiamine deficiency was demonstrable or in animals dying as a result of other types of vitamin deficiency or in animals in which inanition alone was produced. Sykes and Alfredson [13] found electrocardiographic abnormalities in calves fed for long periods on diets deficient in potassium, and Sykes and Moore [14]

6. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, Am. J. Path. **18**:109, 1942.

7. Franz, G.: Eine seltene Form von toxischer Myokardschädigung, Virchows Arch. f. path. Anat. **296**: 743, 1937.

8. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104, 1937.

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10. Follis, R. H.; Orent-Keiles, E., and McCollum, E. V.: Production of Cardiac and Renal Lesions in Rats by a Diet Extremely Deficient in Potassium, Am. J. Path. **18**:29, 1939.

11. Follis, R. H.: Myocardial Necroses in Rats on a Potassium-Low Diet Prevented by Thiamine Deficiency, Bull. Johns Hopkins Hosp. **71**:235, 1942.

12. Thomas, R. M.; Mylon, E., and Winternitz, M. C.: Myocardial Lesions Resulting from Dietary Deficiency, Yale J. Biol. & Med. **12**:345, 1940.

13. Sykes, J. F., and Alfredson, B. V.: Studies on the Bovine Electrocardiogram, Proc. Soc. Exper. Biol. & Med. **43**:575, 1940.

14. Sykes, J. F., and Moore, L. A.: Lesions of Purkinje Network of the Bovine Heart as a Result of Potassium Deficiency, Arch. Path. **33**:467 (April) 1942.

reported degenerative lesions in the Purkinje fibers of those calves; no lesions were found elsewhere in the myocardium. Various authors [15] have suggested that overtreatment of Addison's disease with adrenal cortex preparations might so lower the serum potassium level as to produce myocardial lesions similar to those found experimentally in studies of potassium deficiency, but references to such lesions have not been found. That potassium deficiency due to defective diet alone might occur in man seems unlikely in view of the widespread occurrence of that element in almost all foods consumed by man.

The existence of deficiency of any specific dietary factor in the present case cannot be proved, but the repeated diagnosis of malnutrition on the patient's several admissions to the hospital established beyond doubt the fact of an inadequate diet. Moreover, the patient's excellent response to high vitamin B intake, high caloric diet and other supportive measures during her second stay in the hospital further indicates the probability of vitamin deficiency. On her last admission the patient received large doses of thiamine intramuscularly and by mouth without noticeable benefit; this is contrary to the usual experience when the diagnosis of beriberi heart has been made. It is reasonable to suppose that a heart so badly damaged as that of the present patient could not respond in the usual satisfactory way. The acute and chronic noninfective myocarditis encountered in this case resembles closely the myocardial lesions of experimental thiamine or potassium deficiency as described by the investigators already cited. While there is no electrocardiographic or chemical evidence in the present case either favoring or denying the remote possibility of potassium deficiency, the clinical evidence is such as to indicate not only the possibility but the probability of vitamin deficiency. Since it is possible to exclude with considerable certainty all of the other etiologic factors hitherto incriminated in cases of isolated myocarditis, there appear to be good grounds for casting something more than mere suspicion on deficiency of thiamine as the principal etiologic factor in the present instance of diffuse isolated myocarditis, since this is the one dietary factor deficiency of which has been shown experimentally to be capable of producing similar cardiac lesions.

15. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**:1725 (Nov. 4) 1939. Follis.[11]

SUMMARY

A 15 year old girl who had a history of prolonged malnutrition died of diffuse isolated myocarditis. Heart disease was known to have existed for at least six months before death. Severe failure of the right side of the heart was progressive; left bundle branch lesion, heart block and ventricular fibrillation preceded death.

The heart showed dilatation and hypertrophy, with acute, subacute and chronic, noninfective inflammatory lesions diffusely distributed throughout all parts of the myocardium. These lesions were most extensive in the inner third of the myocardium, and in places they encroached on the endocardium. Mural thrombi were found in both auricles and in both ventricles.

None of the etiologic agents usually incriminated in cases of isolated myocarditis was a factor in this instance. The possibility that the myocardial lesions may have been incited by prolonged dietary deficiency is suggested by the history of prolonged malnutrition and by the resemblance of the lesions to lesions experimentally produced as described in recent literature. Deficiency of thiamine is particularly suspected.

Dr. G. Lyman Duff assisted in the study of this case and in the preparation of the manuscript.

FATAL SPONTANEOUS POTASSIUM INTOXICATION IN PATIENTS WITH UREMIA

JOHN F. MARCHAND, M.D., AND CLEMENT A. FINCH, M.D.

BOSTON

Cardiac arrest due to an increase in the potassium of the serum to toxic levels has not been demonstrated in uremic patients who have maintained a large volume of urine up to the time of death. On the other hand, it has been shown that such arrest does occur regularly in dogs with ligated ureters.[1] Cardiac arrest by the action of potassium was also observed in 2 patients with oliguria and anuria complicating severe nephritis.[2] One of these patients had spontaneous elevation of the potassium of the serum to a level almost as high as that present at death. As each patient had received additional potassium salts, it was not possible to attribute death exclusively to the type of spontaneous potassium intoxication observed in dogs with experimental anuria.

In the cases to be described here potassium intoxication resulted from oliguria and failure of renal excretion. No potassium was given other than that contained in the diet and in the blood which was transfused into the first patient. The second patient did not have a blood transfusion and took no food during the week before death. For each patient the electrocardiograms and the levels of potassium of the serum immediately before death were comparable to those previously observed in association with fatal potassium intoxication in dogs [1] and in man.[2]

REPORT OF CASES

CASE 1.—*History.*—A housewife aged 24 entered the hospital because of nausea and vomiting. Eleven years before, after an appendectomy, a diagnosis of renal ptosis was made and fixation of the left kidney carried out at another hospital. A month later, and repeatedly thereafter, a perirenal abscess was drained from the left flank. In the intervals between recurrences of the abscess there was continued pyuria, but the patient was otherwise well. Three weeks before admission a cystoscopic examination was performed at a local hospital because of sudden hematuria. The retrograde pyelogram of the right side appeared normal, but a catheter could not be inserted in the left ureter, and phenolsulfonpthalein was not excreted by either kidney. After another recurrence and drainage of the abscess, the patient returned home, but suffered from epistaxis and increasing dyspnea with palpitation. Two days before the present admission pain appeared for the first time in the right costovertebral angle. This was accompanied by nausea, vomiting and abdominal distention. There was severe headache with vertigo. The face, hands and feet became swollen, and there was pronounced oliguria, with dark urine.

Examination.—The patient appeared ill and confused. Respirations were rapid and deep, and the breath was uriniferous. The mucous membranes were pale, and the skin was yellow, dry and scaly. There were pitting edema to the waist and puffiness of the face and hands. Only minimal changes were present in the optic fundi. The lungs were free from rales. The heart was enlarged. A loud, blowing systolic murmur was heard at the apex. The systolic blood pressure measured 130 mm. of mercury and the diastolic 100 mm., and the venous pressure was 150 mm. of water. The abdomen was distended, and a draining sinus was present in the left flank. The neurologic examination revealed nothing abnormal save for a weakly positive Chvostek sign.

Laboratory Data.—During eleven days in the hospital the hemoglobin (method of Schales) increased from 6.2 to 6.9 Gm. per hundred cubic centimeters, after transfusions. The white blood cell count ranged from 7,000 to 13,000. The blood smears and differential counts were not remarkable. The urea nitrogen of the blood rose from 107 to 166 mg., and the nonprotein nitrogen from 155 to 208 mg., per hundred cubic centimeters. The protein content of the serum increased from 7 to 7.9 Gm. per hundred cubic centimeters. On the fourth day it was 6.6 Gm., of which 2.9 Gm. was albumin and 3.7 Gm. globulin. The fasting blood sugar was 143 mg. per hundred cubic centimeters. The carbon dioxide content of the plasma ranged from 12.9 to 21.5 millimols per liter, and was 15.9 millimols per liter on the day of her death. On the second day the calcium of the serum was 4.5 milliequivalents per liter; the phosphorus, 3.3 millimols per liter, and the sodium, 129 milliequivalents per liter. Five specimens of urine were collected: The reaction was alkaline; the specific gravity was 1.010; the reaction for albumin was 3 plus, and many red and white cells and occasional casts were present. A heavy growth of Bacillus coli was cultured from the urine, and a mixed growth of Staphylococcus aureus and Streptococcus haemolyticus B was obtained from culture of material from the wound in the left flank.

Course.—The oral temperature reached 100 F. during the first week and then fell. The pulse rate remained

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This work was done under the auspices of the University Committee on Pharmacotherapy.

1. Hoff, H. E.; Smith, P. K., and Winkler, A. W.: The Cause of Death in Experimental Anuria, J. Clin. Investigation **20**:607 (Nov.) 1941.

2. Finch, C. A., and Marchand, J. F.: Cardiac Arrest by Action of Potassium, Am. J. M. Sc. **206**:507 (Oct.) 1943.

near 100 a minute, and the respiratory rate decreased from 30 to 20 a minute. The blood pressure did not change appreciably. An electrocardiogram on the second day was normal except for low voltage (fig. 1*A*). There were continued nausea, vomiting, restlessness and confusion. Peripheral edema slowly increased, and bilateral hydrothorax and pericardial effusion developed. Involuntary twitching of the extremities occurred during the last four days of life. Digitalis was given, together with small amounts of dextrose and isotonic solution of sodium chloride by intravenous injection. With increasing edema and evidence of pulmonary congestion, injection of the saline solution was discontinued, and thereafter, for six days, the fluid intake by mouth amounted to about 1 liter a day. A total of 280 cc. of blood was given in four small transfusions, each transfusion being terminated by an attack of dyspnea and substernal oppression. The output of urine averaged 70 cc. a day for five days; it then decreased and was virtually zero for three days. On the last day the patient became apprehensive and said she was dying. The twitching had increased, and she stated that she "felt funny all over." Although restless, she could remain quiet during examinations and was able to follow instructions. The eyes were prominent and rolling, and there were variations in the level of awareness. Consciousness was not lost until a few moments before death, when the heart beat had become infrequent and irregular. Respiration continued beyond the time when effective cardiac contractions occurred, and it ceased as a result of pulmonary edema two minutes before the final cessation of cardiac activity. The continuous electrocardiogram showed a three minute period of restoration of regular rhythm, accompanied by a palpable peripheral pulse, forty-four seconds after the beginning of a slow intravenous injection of calcium gluconate (figs. 1, 2 and 3).

Autopsy.—The heart weighed 460 Gm. It had stopped in diastole and was distended with blood. There were a thick, yellow, fibrinous deposit on the visceral and the parietal pericardium and an effusion of 400 cc. of clear reddish fluid in the pericardial sac. A postmortem

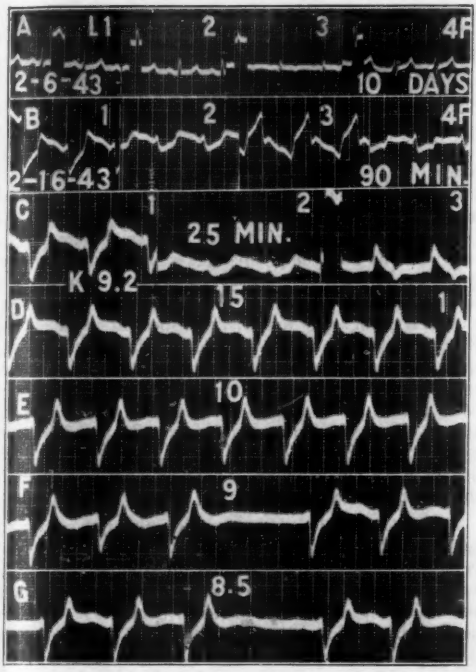

Fig. 1 (case 1).—Electrocardiographic changes preceding cardiac arrest by action of potassium poisoning. Ten days before death tracings from the standard leads were normal except for low voltage (*A*). An hour and a half before death intraventricular block was pronounced, with curves of the right bundle branch block type, and the heart rate was 94 a minute (*B*). A continuous tracing recorded a succession of changes; arrest of the auricles, with loss of P waves and persistence of regular rhythm (*C*, *D* and *E*); a dropped beat (*F*), and, finally, increasing intervals of asystole, during which the complexes appeared in groups of two or three (*G*).

In this figure, and in the accompanying figures, the initial tracings were recorded on a Sanborn "Cardiette," and the continuous electrocardiograms, on an apparatus designed by Dr. W. B. Likoff, graduate assistant in medicine at the Peter Bent Brigham Hospital, and Mr. M. B. Rappaport, research engineer, Sanborn Instrument Co., Cambridge, Mass. (Am. Heart J., to be published). Each full strip on the figure represents six seconds. Standardization of deflections: *A* and *B*, 1 cm. = 1 millivolt; *C* to *G*, 2 cm. = 2 millivolts. On each record, the number of the lead is in the upper right corner, and the time before death, at the center.

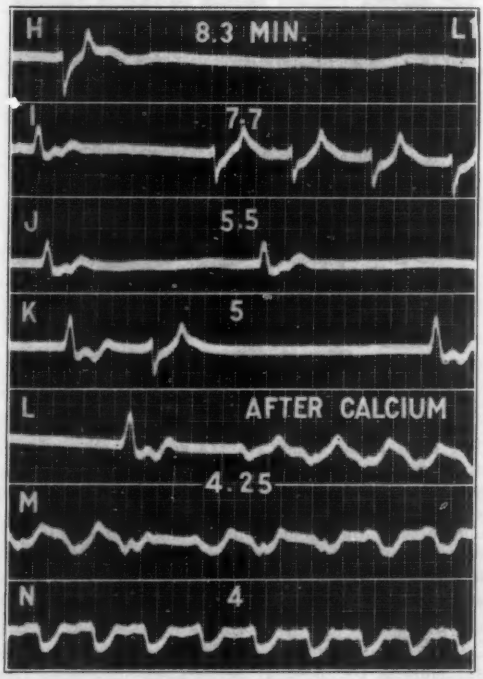

Fig. 2 (case 1).—Effect of calcium (lead I). The periods of asystole increased to as long as nine seconds, and the duration of the complexes was greatly prolonged (*H*). The direction of the complexes varied with changes in the degree of block in conduction on the two sides of the heart (*I*, *J* and *K*). Regular rhythm was resumed after the intravenous injection of calcium gluconate (*L*, *M* and *N*).

roentgenogram of the heart showed no intracardiac calcification, and microscopic sections showed no evidence of vascular disease or myocardial infarction. The lungs were edematous but not consolidated. Their respective weights were 680 and 520 Gm. The left kidney was small and inseparable from a mass of scar tissue adherent to the vertebrae. It was composed of multiple loculi of purulent and necrotic material, each one continuous with the draining sinus in the left flank. The remains of a dilated renal pelvis communicated with a ureter occluded by fibrous tissue near the hilus of the kidney. The right kidney weighed 300 Gm. The capsule stripped easily. On cut section it appeared blood streaked and edematous. Microscopic examination revealed subacute glomerulonephritis with involvement of all the glomeruli in varying degrees (fig. 4).

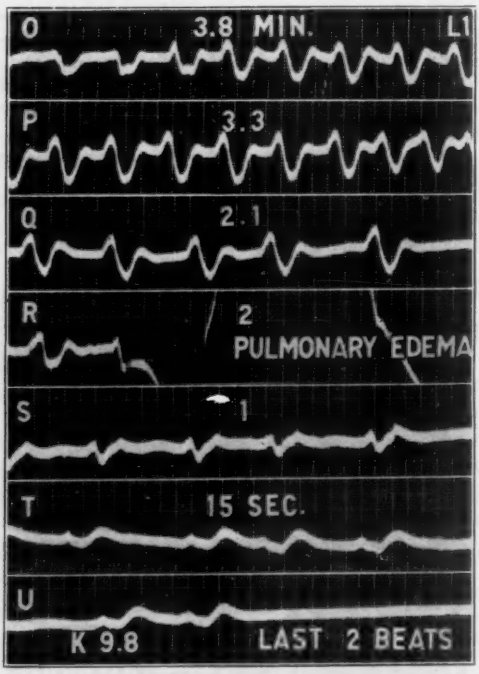

Fig. 3 (case 1).—Final stages of arrest (lead I). The overlapping complexes (*O* and *P*) gave the appearance of a circus movement, but each impulse was actually separate, as seen in (*Q*), where the overlap was eliminated by slowing of the rate from 90 to 50 a minute. At the moment that pulmonary edema prevented further respiration there was struggling (R), followed by a few terminal microsystoles (*S* and *T*) and final cardiac arrest (*U*).

Case 2.[3]—*History.*—A labor union secretary, aged 41, entered the hospital because of drowsiness and headaches. Ten years previously he had passed a life insurance examination; at that time, however, he was beginning to feel below par, and a diagnosis of hypertension and Bright's disease was made at another hospital. Thereafter, he had had nocturia for several years, frequent headache and vomiting for two years and failing vision, muscular twitching and decline in weight, from 235 to 178 pounds (106.6 to 80.7 Kg.), for six months. For a month he had also had episodes of dyspnea on exertion, paroxysms of nocturnal dyspnea and occasional nosebleed. The face appeared slightly puffy, and there was itching of the skin. Mental confusion became evident in the last week of life. At the time of admission there were epistaxis, of several hours' duration, headache and pain in the chest.

Examination.—The patient was large and ruddy. He appeared drowsy and confused. The skin was telangiectatic over the cheeks and dry and yellow in general. A powdery scale was present about the eyes and over the arms. There was a stare characteristic of nephritis. In the optic fundi the nerve disks were elevated and indistinct. The retinal arteries were narrow and tortuous and compressed the veins at intersections. There were retinal scars, patches of exudate and hemorrhages in all stages. Visual acuity was 20/200, and newsprint was not distinguished at close range. Dentition was poor; the tongue was brown and furry, and the mucous membranes were pallid. A few moist rales were heard over the lower posterior field of both lungs. The heart was enlarged, and the aortic second sound was loud and ringing. The blood pressure was 225 systolic and 190 diastolic. The abdominal organs were not palpable. There was muscular twitching of the extremities.

Laboratory Data.—On admission the red cell count was 3,600,000, and the white cell count, 10,000 per cubic millimeter, with a normal differential count. The hemoglobin decreased in five days from 11.3 to 9.7 Gm. per hundred cubic centimeters (Schales). On the second day the nonprotein nitrogen of the serum was 258 mg. per hundred cubic centimeters, and the total protein, 7.4 Gm. per hundred cubic centimeters, of which 3.8 Gm. was albumin and 3.6 Gm. globulin. The urea nitrogen of blood on the fifth day measured 163 mg. per hundred cubic centimeters. The chloride of the serum was 96 milliequivalents per liter on the second day; the calcium of the serum measured 4 millimols per liter on the second day and 3.7 millimols on the fifth day. The specimens of urine were yellow and acid on the first three days and were alkaline and brownish or bloody thereafter. The specific gravity was fixed at 1.010, and the urine gave a 2 plus reaction for albumin and contained numerous red cells, a few white cells and rare hyaline or granular casts. There were occasional small blood clots.

Course.—The patient lived ten days after admission but vomited repeatedly and was unable to take food. He was sufficiently lucid to recognize persons and converse until the last day, but was continually confused and restless. An electrocardiogram on the fourth day indicated a left axis deviation. The pulse rate was between 90 and 100 a minute, and the blood pressure remained constant. The respiratory rate was 20 a minute. The intake of fluid was between 1,100 and 1,600 cc. a day, most of which was given as 5 per cent dextrose by clysis. The volume of urine averaged 660 cc. a day for a week and then decreased to about half that amount. In the last four days the bladder was emptied by catheterization because of failure to void. During this interval there were periods of profound drowsiness, with intermittent respiration. Fourteen hours before death there was a uremic frost. A succession of changes appeared in the electrocardiogram (figs. 5, 6 and 7), and the patient gradually lapsed into an unresponsive state, during which he squirmed about, fumbled with his hands and muttered repetitious syllables with each

3. The study of this case was made possible through Dr. James P. O'Hare.

breath. The Cheyne-Stokes respiration continued, but the blood pressure did not fall until increasing intervals of asystole had appeared on the electrocardiogram, just before final cardiac arrest. In the last hours of life the heart sounds had become faint, prolonged and swishing. The skin was moist, but there was no venous distention or edema. Four minutes before the last electrical impulse was recorded no peripheral pulse could be felt, and the blood pressure could not be measured. Respiration ceased two minutes later.

The table gives values for potassium in the 2 cases.

*Results of Determinations of Potassium in Two Cases of Uremia**

Source	Value, mEq./L.
Case 1	
Serum 20 min. before death	9.2
Serum from heart blood at death	9.8
Spinal fluid at death	4.5
Pericardial fluid at death	9.0
Case 2	
Serum 6 days before death	5.8
Serum 13½ hr. before death	8.8
Serum 3¾ hr. before death	9.2
Serum from heart blood at death	10.1
Spinal fluid at death	4.5
Pericardial fluid at death	8.8
Urine 5 days before death	52.5
Urine 1 day before death	49.8
Urine from bladder at death	52.5
Total potassium excreted in urine:	
315 cc. 5 days before death.... 16.5 mEq. (0.064 Gm.)/24 hr.	
300 cc. 1 day before death..... 14.9 mEq. (0.058 Gm.)/24 hr.	
65 cc. last day of life..... 3.4 mEq. (0.013 Gm.)/11 hr.	

* Specimens of blood were collected under oil, and the serum was separated at once. No hemolysis occurred. The analyses for potassium were made by Dr. A. W. Winkler, of the department of medicine, Yale University, according to Hald's modification of the chloroplatinate method of Shohl and Bennett (Hald, P. M.: Determination of the Bases of the Serum and Whole Blood, J. Biol. Chem. **103**: 471 [Dec.] 1933). To convert milliequivalents of potassium per liter to milligrams per hundred cubic centimeters, the value for the former is multiplied by 3.9.

COMMENT

In each of these cases the development of a high concentration of potassium in the serum was associated with failure of renal excretion sufficient to produce other evidence of azotemia as well. This was represented in the first case by the evidence of loss of chloride, sodium and calcium and by retention of phosphate and nitrogenous substances. The oliguria, and finally the anuria, of the last two weeks of life was the result of glomerulonephritis involving the remaining right kidney, apparently a complication of the infection with Str. haemolyticus B in the left flank. There was no indication of any toxic effect from potassium until after this interval of oliguria, and it is evident that there was no significant failure in excretion of potassium until after failure of water excretion had begun. Not even the earliest effect of an increase in the potassium of the serum, which is a heightening of the T wave,[4] had appeared until after the volume of urine had decreased. As extrarenal excretion of the substance is negligible, the failure of excretion of potassium was shown in case 1 by the progression from oliguria to virtually complete anuria and in case 2 by the presence in the urine of only a small fraction of the amount of potassium normally excreted by the kidney.

The three sources from which the high concentration of potassium in the serum appears to have been derived were (*a*) diet, (*b*) red cells introduced by transfusion of blood and (*c*) tissue metabolism. Of these, the last in itself has regularly sufficed to cause death of animals with experimental anuria.[1] There was no evidence that any unusual amount of intracellular potassium was liberated as a result of destruction of the patient's body tissues.

In the second case the elevated level of potassium appears to have been derived largely from tissue metabolism, since no transfusion was given and no food was taken in the last week of life. The course in this respect was comparable to that of anuric dogs which die of potassium intoxication even in the absence of any dietary intake. The course differed in that the suppression of potassium excretion was more gradual and there was no complete cessation of water excretion.

It has not been possible to demonstrate by chemical methods alone that potassium may be an actual cause of death from uremia in man. However, toxic effects from impaired excretion of potassium and the resulting high levels in the blood have been suggested by a series of observers, and the earlier data on the frequent tendency to retention of potassium in patients with renal disease have been currently reviewed and amplified.[5]

Symptoms attributed to high levels of potassium in the serum include the paresthesia and weakness which were experienced in case 1 and which have been reported to follow large oral doses of potassium salts.[6] There was no evidence that the persistent vomiting in the 4 reported cases of fatal potassium intoxication was caused by potassium, although the authors also observed vomiting in intact dogs killed by the slow intravenous infusion of solutions of potassium chloride. The flaccid quadriplegia which accompnaied fatal potassium intoxication in 2 instances [2] did not occur in these cases, and the actual role of potassium in relation to such paralysis remains obscure. In each case a disturbance in the level of other electrolytes and metabolites in the blood also contributed to the symptoms,

4. Thomson, W. A. R.: The Effect of Potassium on the Heart in Man, Brit. Heart J. **1**:269 (Oct.) 1939.

5. Keith, N. M.; King, H. E., and Osterberg, A. E.: Serum Concentration and Renal Clearance of Potassium in Severe Renal Insufficiency in Man, Arch. Int. Med. **71**:675 (May) 1943.

and in the 2 cases cited here the tetanic effect of hypocalcemia may have counteracted any tendency to flaccid paralysis or loss of tendon reflexes.

Neither in experimental animals nor in man does the effect of potassium on the heart result in signs or symptoms of circulatory failure until just before cardiac arrest. The diagnosis must therefore be established by a demonstration of the characteristic changes in the electrocardiogram, accompanied by sufficiently great elevation in the level of potassium in the serum. However, the sequence of electrocardiographic changes alone is sufficiently specific to serve as a basis for the selection of cases in which chemical studies should also be made.

The significant features of the electrocardiograms shown here include elevations and rapid variations in the height of the T waves, changes in the amplitude of the R waves and pauses representing momentary arrest of the sinoauricular node. Shortly before final cardiac arrest there were loss of P waves, due to auricular arrest, idioventricular rhythm and a pronounced delay

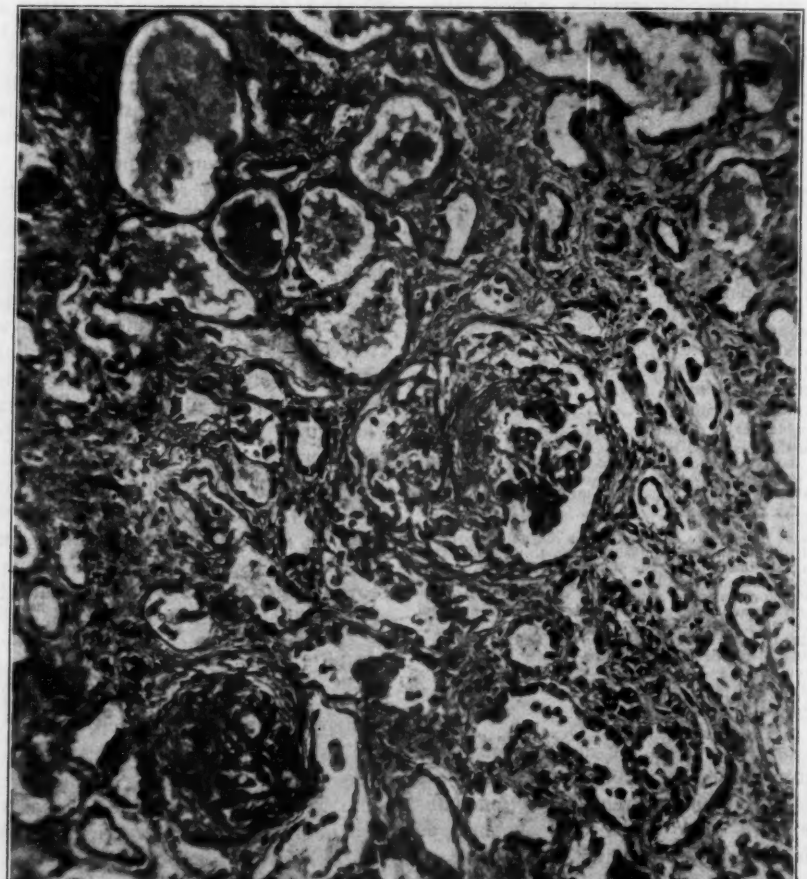

Fig. 4 (case 1).—Right kidney. There are numerous fibrous adhesions between the glomerular tufts and Bowman's capsule, as well as between individual tufts. The tubules are separated by diffusely increased interstitial connective tissue. The tubular epithelium is atrophic. Varied amounts of precipitated protein are seen in the lumens. Phloxine-methylene blue; ×150.

of conduction in the ventricles, with variations in the relative degree of block on the two sides of the heart. The progression of block in ventricular conduction was associated with increase in the voltage of the deflections, elevation of the

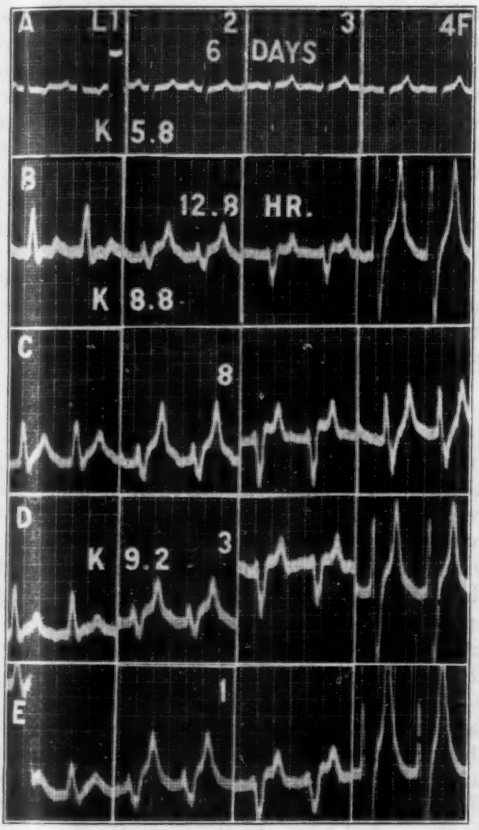

Fig. 5 (case 2).—Serial electrocardiograms in a case of potassium intoxication. A control tracing of the four standard leads six days before death showed an inverted T_1 wave and left axis deviation (*A*). Changes in the fourteen hours preceding death (*B*, *C*, *D* and *E*) included the development of intraventricular block, with curves of the right bundle branch block type and a progressive increase in the duration of the individual deflections and the complexes as a whole. There were variations in voltage and a decrease in the amplitude of the R waves, accompanied by a notable increase in the height of the T waves. Deflections in lead IV finally exceeded the width of standard electrocardiograph paper. Auricular arrest is indicated by the gradual depression and loss of P waves.

In *A*, 1 cm. = 1 millivolt; in *B* to *E*, 3 cm. = 1.5 millivolts.

portion of the complexes derived from the T waves, displacement of the portions derived from the S-T segments, overlapping between successive complexes and between portions within the complexes and transition from sharp to smooth and flowing contours. Altogether, in these 2 cases the ventricular complexes increased in duration from three-tenths and four-tenths second respectively ten and six days before death to three-fourths second or more at the time of arrest. The changes in the standard leads (figs. 1 *B* and *C* and fig. 5) were of the type interpreted according to Wilson's criteria as evidence of right bundle branch block, but did not result from disease of the coronary arteries to which such changes are frequently attributed. Continued, but slow, circulation of the blood in the moment prior to cardiac arrest was shown in case 1 by the effect which became apparent forty-four seconds after the beginning of an intravenous injection of calcium gluconate. The calcium ions temporarily restored a regular rhythm and normal rate. Such electrocardiographic changes as would have resulted from the pericarditis with effusion were

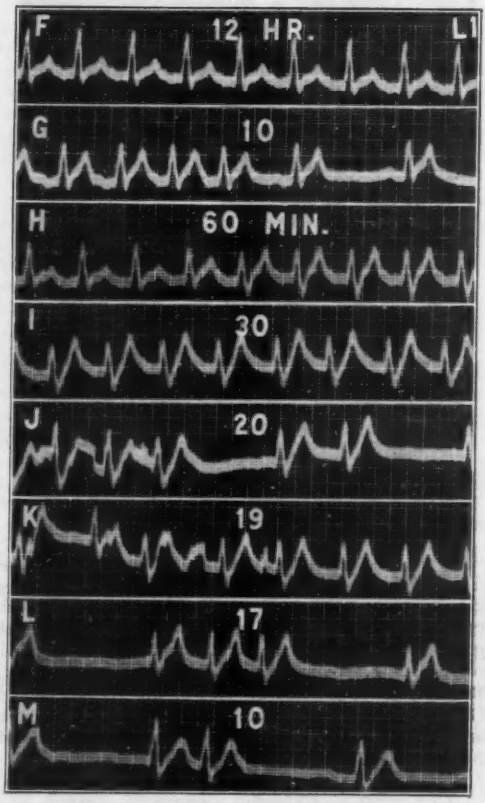

Fig. 6 (case 2).—Stages preceding cardiac arrest. Lead I, in the last twelve hours of life, showed: prolonged, overlapping complexes (*F*); momentary pauses of the sinoauricular node prior to auricular arrest (*G*); changing block, with rapid variations in the R, S and T waves (*H*), and an amplitude of the T waves finally exceeding that of the R waves (*I*). Twenty minutes before death there appeared increasing intervals of arrest, during which the P waves appeared to be depressed and then lost and complexes began to appear singly and in small groups (*J*, *K*, *L* and *M*).

entirely masked by the more striking effects of potassium intoxication.

The concentrations of potassium in the serum of 9.8 and 10.1 milliequivalents per liter in the 2 cases represent an increase to an amount twice that normally present. This level is in the lower portion of the range of values at which cardiac arrest has been observed in experiments on dogs.[1] It may be compared with the previously reported level for man of 8.85 milliequivalents per liter reached spontaneously and 10.5 milliequivalents

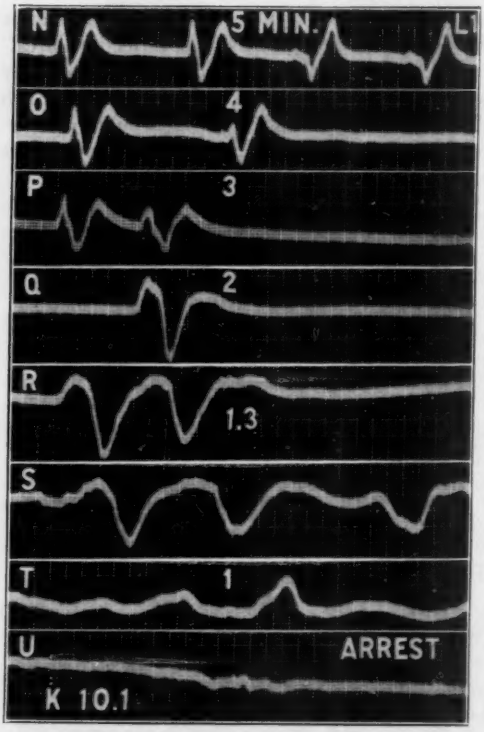

Fig. 7 (case 2).—Arrest of heart (lead I). There was a momentary reappearance of P waves five minutes before cardiac arrest, at a time when the rhythm was regular and the rate 40 per minute (*N*). Maximal spreading is seen in the single and paired terminal complexes, which appeared at regular, but infrequent, intervals during the last minutes of life (*O*, *P*, *Q* and *R*). The last impulse continued as a circus movement for slightly over a minute before becoming exhausted (*S*, *T* and *U*).

per liter at death.[2] The 9 and 8.8 milliequivalents per liter for the pericardial fluid may represent a lower level for the serum while the effusion was forming. The level of 4.5 milliequivalents per liter for the spinal fluid in the 2 cases differs from the levels for the serum but is higher than the amount ordinarily present.

In 2 previously described cases of potassium intoxication,[2] and in the first of the 2 cases described here, consciousness was retained until immediately before death. Our second patient had become stuporous in his final hours, apparently as a result of administration of barbiturates. In all 4 cases an abrupt circulatory failure preceded the cessation of respiration and in the 3 cases in which autopsy was done the heart had stopped in diastole. In our last case the heart was sufficiently dilated to permit the collection of a large specimen of blood. The cause of the renal failure was severe nephritis in all but the last case, in which it was malignant nephrosclerosis. As there is no indication that potassium intoxication is a specific effect of these diseases, it may also be expected to occur in association with advanced renal failure from other causes.

SUMMARY

Fatal spontaneous potassium intoxication occurred in 2 cases of uremia with renal failure and oliguria. The failure in excretion of potassium resulted in an increase in the concentration of potassium in the serum to 9.8 and 10.1 milliequivalents, while the concentration in the pericardial fluid was 9 and 8.8 miliequivalents and that in the spinal fluid 4.5 milliequivalents per liter at death. Serial electrocardiograms showed the characteristic changes leading to cardiac arrest by the action of potassium, including evidence of auricular arrest and progressive delay of conduction in the ventricles. The symptoms were those usual with uremia. Consciousness persisted up to the time of death in the first case, but became clouded in the second case. In the first case the intravenous injection of a solution of calcium gluconate resulted in transient restoration of regular rhythm. The cessation of respiration in each case was preceded by circulatory failure, and there was evidence that the heart was arrested in diastole.

Dr. Alexander Winkler made the analyses for potassium, and Dr. William B. Likoff gave us the use of his continuously recording electrocardiograph.

Peter Bent Brigham Hospital.

6. Arden, F.: Experimental Observations upon Thirst and on Potassium Overdosage, Australian J. Exper. Biol. & M. Sc. **12**:121 (Sept.) 1934. Keith, N. M.; Osterberg, A. E., and Burchell, H. B.: Some Effects of Potassium Salts in Man, Proc. Staff Meet. Mayo Clin. **17**:49 (Jan. 28) 1942; Ann. Int. Med. **16**: 879 (May) 1942. Thomson.[4]

VITAMINS A, B AND C IN DIABETIC CHILDREN

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The results of an investigation made in the summer of 1941 on the vitamin status of the diabetic children at the summer camp of the New York Diabetes Association have been reported.[1] In 1942 the observations were repeated because it was felt that the first effort was fragmentary and that a more satisfactory and complete survey could be accomplished with an increase in laboratory personnel and equipment and with improved methods. In the present paper the results obtained in the second study are reported.

CLINICAL MATERIAL

One hundred and fourteen juvenile diabetic subjects from 6 to 18 years of age, except for 2 aged 20 and 26 respectively, were studied. They were about equally divided as to sex. The children came in four successive groups during July and August 1942, each group spending two weeks at the camp. They were largely patients of the diabetes clinics in Greater New York, though a few were referred by individual physicians. Except for diabetes they had no physical ailments. A medical history was taken of each child, in which were recorded the duration of the disease, the success achieved in control of the diabetes, the dose of insulin, the diet prescribed and the growth status. Daily checks were made on the urine, the physical condition, the diet and the dose of insulin while the child was at the camp. The data were then correlated with the results of the vitamin determinations. Eleven normal young adults, members of the camp staff, served as controls.

METHODS

The clinical criteria for deficiency were those generally accepted: Vitamin A deficiency was diagnosed by inspection of the epithelial tissues (xerosis conjunctivae and keratosis pilaris). Thiamine (vitamin B_1) deficiency was considered to be present if chronic fatigue, diminished intensity or absence of the ankle or the knee jerk, tenderness of the muscles of the calf or sensory disturbance (alteration in touch, pain or vibratory sense) was demonstrated; chronic fatigue alone was not regarded as warranting a diagnosis of vitamin B_1 deficiency. Ariboflavinosis was revealed by the presence of scaly blepharitis, cheilosis or smoothness of the tongue, with or without denudation. The diagnosis of avitaminosis C on the basis of physical signs proved unsatisfactory. The adequacy of the Rumpel-Leede tourniquet test has been discredited in recent publications; in our experience the results of the test did not parallel the occurrence of "chemical scurvy." None of our patients had clinical evidence of scurvy. Gums which were swollen or bled easily were prevalent, and it was impossible to be certain whether poor dental hygiene or lack of vitamin C was responsible for these abnormalities.

The amounts of carotene and vitamin A were determined with the Klett-Summerson photoelectric colorimeter. The method was based on the Clausen-McCord extraction and the Carr-Price reaction; the modification by Sinay [2] will be published elsewhere. The specimens were protected from light from the time of venipuncture to the final reading. Four cubic centimeters of plasma was extracted, the carotene content determined, the extract dried under a stream of oil-pumped nitrogen and the amount of vitamin A estimated. Standardization curves were based on a series of concentrations of pure crystalline vitamin A and 100 per cent carotene (90 per cent β-carotene). A correction curve was used to compensate for any blue color in the final reaction due to carotene. The results were expressed in micrograms of carotene or vitamin A per hundred cubic centimeters of plasma.

The ascorbic acid levels of the plasma were determined titrimetrically according to the procedure of Farmer and Abt.[3] Two cubic centimeters of plasma was precipitated immediately with 6 per cent metaphosphoric acid, and the filtrates were stored at 5 C. until titrated, about three hours later.

Cholesterol levels in the plasma were estimated by the Bloor extraction method,[4] with color development under temperature control as described by Ireland.[5]

NORMAL VALUES

The carotene content of plasma ranged from 272 to 139 micrograms, with a mean value of 195 micrograms. The vitamin A level varied from 71 to 40 micrograms, with a mean value of 50 micrograms. The normal vitamin A–carotene ratio fell sharply between 0.28 and 0.21.

From Camp Nyda, conducted by the New York Diabetes Association, Inc.

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Mr. Felix Morgenstern donated a photoelectric colorimeter for use in the determinations.

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4. Bloor, W. R., and Knudson, A.: The Separate Determination of Cholesterol and Cholesterol Esters in Small Amounts of Blood, J. Biol. Chem. **27**:107-112, 1916.

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The normal value for the ascorbic acid content of plasma is not finally established; we have accepted figures above 0.8 mg. per hundred cubic centimeters of plasma as representative of tissue saturation and values between 0.8 and 0.4 mg. as indicative of tissue unsaturation; a level of less than 0.4 mg. has been regarded as critical, and as evidence of chemical scurvy.

The normal range for the cholesterol content of the plasma for the method used is 100 to 230 mg. per hundred cubic centimeters.

RESULTS

The results of the chemical and physical examinations are given in the table.

Carotene.—Twenty-eight per cent (32) of the 114 diabetic children in this series showed a carotene content of the plasma above the normal, and 17 per cent (19 children), a content below the normal. In the subgroups, the same carotene pattern was evident throughout, with noteworthy deviations from it of an increased and a decreased carotene content of the blood.

Hypercarotenemia: Forty per cent of the diabetic children exhibiting hepatomegaly, 40 per cent of those with associated cholesteremia and 60 per cent of those with a positive reaction to the tourniquet test (the number of children, 5, with a positive reaction to this test was too small to make possible any valid conclusions concerning this group, and data for them will be omitted in the further discussion of plasma carotene) showed an increase of carotene in the plasma.

Hypocarotenemia: Ten per cent of the diabetic children with a history of glycosuria and frequent or recent acidosis, 10 per cent of the children with hepatomegaly, none of the children with signs of vitamin A deficiency and 3 per cent of the children with cholesteremia showed a reduction in the carotene content of the blood. None of the subjects had infections, which Clausen and McCoord [6] found to be a cause of hypocarotenemia.

In previous reports, as a rule, the carotene level of the blood has been stated to be elevated. Two other investigators have reported on series of 100 or more cases of diabetes, that is, a number comparable to ours. Rabinowitch [7] demonstrated an excess of carotene in the blood in 426 of 500 cases of diabetes, that is, in 85.2 per cent, and Boeck and Yater,[8] in 86 per cent of 100 cases. In the present series only 32 (28 per cent) of 114 diabetic children showed high carotene levels of the blood. More recent contributions have given evidence of lower values for carotene, which are not so consistently above the normal as those cited in earlier analyses. In this connection, the statement of Gordon and Sevringhaus [9] may be quoted: "There is no characteristic pattern in the carotene–vitamin A relationship," a statement which implies (personal communication) that they found a considerable scattering of high and low carotene values among the diabetic patients whom they studied. Thus it appears that as the management of diabetes has progressed, the frequency of hypercarotenemia among patients with diabetes has become less. We believe this can be explained on the basis of better utilization and digestion of fat and a lower incidence of hyperlipemia than existed a decade ago.

From our results (table) it is evident that among diabetic patients exhibiting hepatomegaly, that is, those presumably with fatty infiltration of the liver, or an excess of cholesterol in the blood, the occurrence of hypercarotenemia was much more common and that of hypocarotenemia less frequent than among the diabetic children as a whole. This indicates that when there is a disturbance in the fat metabolism in diabetes, carotene is likely to accumulate in the blood. The small number of cases of hypocarotenemia among the diabetic patients with a history of glycosuria and frequent or recent acidosis bears out the idea that with the accumulation of lipid substances associated with diabetes a mobilization of carotene in the blood occurs.

The cause of hypercarotenemia in diabetes was postulated by Ralli and associates [10] as being an impairment of the function of the liver to convert carotene into vitamin A and the consequent accumulation of carotene within the body. Moore [11] concluded:

> The observation of high vitamin A reserves in the livers of subjects dying from diabetes must rule out the suggestion that there is any serious impairment of the power of the liver to convert carotene into vitamin A.

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Subjects	Type of Data	Plasma Carotene, Micrograms per 100 Cc.	Plasma Vitamin A, Micrograms per 100 Cc.	Plasma Vitamin A-Carotene Ratio	Plasma Vitamin C, Mg. per 100 Cc.	Plasma Cholesterol, Mg. per 100 Cc.
Normal (11).....	Mean.....	195	50	0.26		
	Range.....	272-139	71-40	0.28-0.21	2.0-0.8*	230-100*
	Standard deviation..	±39	±10	0.07		
Diabetic (114).....	Mean.....	231	36	0.18	0.87	204
	Range.....	420-62	57-16	0.56-0.06	1.74-0.21	454-90
	Standard deviation..	±78	±8	0.09	±0.29	±59
	Per cent abnormal...	28% above 275 17% below 140	None above 71 68% below 40	11% above 0.28 67% below 0.20	39% between 0.8 and 0.4 4% below 0.4	26% above 230 2% below 100
History of good control of diabetes (58)	Mean.....	226	35	0.19	0.91	219
	Range.....	420-62	57-20	0.56-0.06	1.74-0.21	454-90
	Standard deviation..	±85	±8	0.11	±0.29	±36
	Per cent abnormal...	31% above 275 19% below 140	None above 71 69% below 40	21% above 0.28 64% below 0.20	40% between 0.8 and 0.4 3% below 0.4	24% above 230 0.2% below 100
History of persistent glycosuria (35)	Mean.....	233	36	0.16	0.82	202
	Range.....	406-98	55-16	0.30-0.08	1.71-0.22	335-93
	Standard deviation..	±80	±8	0.05	±0.29	±48
	Per cent abnormal...	26% above 275 14% below 140	None above 71 74% below 40	3% above 0.28 74% below 0.20	28% between 0.8 and 0.4 9% below 0.4	20% above 230 0.3% below 100
History of glycosuria and frequent or recent acidosis (21)	Mean.....	235	38	0.17	0.80	216
	Range.....	381-130	53-20	0.34-0.07	1.21-0.22	430-125
	Standard deviation..	±74	±10	0.07	±0.22	±76
	Per cent abnormal...	24% above 275 10% below 140	None above 71 57% below 40	9% above 0.28 57% below 0.20	57% between 0.8 and 0.4 5% below 0.4	43% above 230 None below 100
Diabetes of more than average (4.3 yr.) duration (44)	Mean.....	211	35	0.20	0.63	213
	Range.....	406-62	53-19	0.56-0.06	1.74-0.22	300-125
	Standard deviation..	±82	±8	0.10	±0.37	±42
	Per cent abnormal...	23% above 275 27% below 140	None above 71 70% below 40	16% above 0.28 61% below 0.20	40% between 0.8 and 0.4 2% below 0.4	23% above 230 None below 100
Treated with unmodified insulin (11)	Mean.....	230	36	0.17	0.84	213
	Range.....	329-98	55-22	0.34-0.08	1.21-0.22	265-170
	Standard deviation..	±75	±7	0.06	±0.28	±26
	Per cent abnormal...	36% above 275 18% below 140	None above 71 72% below 40	9% above 0.28 72% below 0.20	36% between 0.8 and 0.4 9% below 0.4	27% above 230 None below 100
Treated with protamine zinc insulin (103)	Mean.....	231	36	0.18	0.87	208
	Range.....	420-62	57-16	0.56-0.06	1.74-0.21	454-90
	Standard deviation..	±79	±8	0.09	±0.29	±62
	Per cent abnormal...	27% above 275 16% below 140	None above 71 68% below 40	12% above 0.28 66% below 0.20	39% between 0.8 and 0.4 4% below 0.4	26% above 230 2% below 100
Signs of vitamin A deficiency (10)	Mean.....	235	33	0.15	0.85	222
	Range.....	360-175	53-24	0.30-0.08	1.24-0.46	268-167
	Standard deviation..	±64	±8	0.09	±0.21	±37
	Per cent abnormal...	30% above 275 None below 140	None above 71 90% below 40	10% above 0.28 80% below 0.20	50% between 0.8 and 0.4 None below 0.4	50% above 230 None below 100
Signs of vitamin B_1 deficiency (20)	Mean.....	251	38	0.17	0.87	220
	Range.....	406-75	53-25	0.40-0.08	1.38-0.22	430-143
	Standard deviation..	±92	±7	0.08	±0.34	±67
	Per cent abnormal...	40% above 275 15% below 140	None above 71 60% below 40	5% above 0.28 65% below 0.20	30% between 0.8 and 0.4 10% below 0.4	35% above 230 None below 100
Signs of riboflavin deficiency (5)	Mean.....	218	38	0.17	0.87	249
	Range.....	296-177	51-27	0.26-0.14	1.25-0.68	297-200
	Standard deviation..	±44	±6	0.04	±0.21	±33
	Per cent abnormal...	20% above 275 None below 140	None above 71 60% below 40	None above 0.28 80% below 0.20	60% between 0.8 and 0.4 None below 0.4	60% above 230 None below 100
Positive tourniquet test (5)	Mean.....	274	34	0.13	0.94	215
	Range.....	360-130	55-23	0.17-0.09	1.74-0.46	268-145
	Standard deviation..	±79	±11	0.03	±0.44	±51
	Per cent abnormal...	60% above 275 20% below 140	None above 71 80% below 40	None above 0.28 100% below 0.20	40% between 0.8 and 0.4 None below 0.4	20% above 230 None below 100
More than 4 inches (10 cm.) under normal height (10)	Mean.....	230	37	0.22	0.97	190
	Range.....	327-98	53-19	0.66-0.08	1.74-0.46	309-134
	Standard deviation..	±91	±10	0.05	±0.34	±48
	Per cent abnormal...	30% above 275 20% below 140	None above 71 60% below 40	20% above 0.28 50% below 0.20	30% between 0.8 and 0.4 None below 0.4	10% above 230 None below 100
Hepatomegaly (20)	Mean.....	245	35	0.17	0.94	208
	Range.....	394-62	51-22	0.47-0.07	1.38-0.58	309-130
	Standard deviation..	±90	±8	0.07	±0.24	±52
	Per cent abnormal...	40% above 275 10% below 140	None above 71 65% below 40	5% above 0.28 65% below 0.20	40% between 0.8 and 0.4 None below 0.4	30% above 230 None below 100
Elevated cholesterol level of plasma (30)	Mean.....	262	39	0.16	0.79	278
	Range.....	381-98	52-25	0.35-0.08	1.46-0.22	454-230
	Standard deviation..	±76	±6	0.06	±0.27	±52
	Per cent abnormal...	40% above 275 3% below 140	None above 71 53% below 40	7% above 0.28 70% below 0.20	46% between 0.8 and 0.4 7% below 0.4	100% above 230 None below 100

* Values accepted in the literature.

Murrill and associates [12] observed that carotene administered orally did not increase the vitamin A content of the blood either in normal or in diabetic subjects. From this observation, together with the fact that the entire group of diabetic patients whom they studied had normal vitamin A values in the blood, they decided that there was no indication that the liver of the diabetic patient converts carotene to vitamin A more slowly than that of the normal person.

The idea that a disturbance of fat metabolism is one of the factors responsible for the accumulation of carotene in the blood of diabetic persons has gradually been gaining ground. The solubility of carotene in fat, the direct ratio of the quantity of carotene taken up through the wall of the intestine to the amount of fat absorbed (Ahmad [13]), the high fat diet of diabetic patients and the tendency to hyperlipemia in such persons, all point to the assumption that where there is an excess of fat there will be an excess of carotene, whether this concerns the process of absorption from the intestine, storage in the liver or accumulation in the blood.

Arguments, both pro and con, concerning the direct relation of hyperlipemia and a high fat diet to carotenemia have been put forward. Rabinowitch [7] observed that pronounced hypercarotenemia was associated with severe diabetes, poor prognosis and hypercholesteremia. (All these conditions favor the presence of hyperlipemia.) On the other hand, Boeck and Yater [8] expressed the opinion that the severity of the diabetes, the character of the diet and the fat content of the blood had no bearing on the occurrence of xanthemia, though xanthosis was found more often in cases of severe diabetes; these statements almost run contrary to Rabinowitch's experience. Heymann [14] showed that utilization of carotene was interfered with in diabetes, a disturbance which, in his opinion, was associated not with hypercholesteremia or hyperglycemia but with some other metabolic disturbance. Ahmad [13] demonstrated that the absorption of carotene was largely influenced by the amount of fat in the diet. Murrill and associates [12] expressed the opinion that high values for carotene in the blood in cases of diabetes could be explained by the presence of a high fat content of the blood in these cases. Josephs [15] demonstrated a direct relation of vitamin A, carotene and the total lipids of the blood. In his experience, the cholesterol parallels the degree of hyperlipemia. He found that diabetic patients without hyperlipemia showed no excess of carotene in the blood. Opinion apparently is divided as to the relation of the absorption and retention of fat and the degree of carotenemia, but the trend of investigation is toward the conclusion that the solubility of carotene in fat aids in the absorption of carotene and determines the extent to which it is present in the blood. In the presence of diabetes, which is often associated with hyperlipemia, a high carotene content may frequently be expected.

Our results—the direct correlation of the carotene level with the degree of cholesteremia and the parallelism between hepatomegaly and hypercarotenemia—support the concept of the dependence of an increase in carotene on its solubility in fat. The more efficient and widespread use of insulin has doubtless resulted in a diminishing incidence of hyperlipemia among diabetic patients, an effect accounting for the less frequent occurrence of hypercarotenemia now than a few years ago. This relation will not be completely understood until further concomitant studies of the lipid and carotene contents of the blood in diabetic subjects are carried out.

Vitamin A.—In no instance was the vitamin A content of the plasma above the normal. More than half the 114 diabetic children studied (68 per cent, or 78) showed a subnormal level of vitamin A in the plasma. As none of the subjects had infections (which Clausen and McCoord [6] stated resulted in lowering of vitamin A), this factor may be eliminated as a cause of the low values for vitamin A. The occurrence of low vitamin A levels of the plasma in a large proportion of children in whom clinical evidence of lack of vitamin A was elicited (10 subjects) bears out the validity of the accepted signs of avitaminosis A. The only other variation of note in the subgroups concerned the subjects with a positive reaction to the tourniquet test, a very large number of whom (80 per cent) had low values for the vitamin A in the plasma. As mentioned in the discussion of carotene levels of the plasma, the number of patients, 5, with a positive reaction to the tourniquet test is too small to justify any final conclusions regarding the relation of plasma carotene or vitamin A to a positive reaction to the tourniquet test.

The notable depression of the vitamin A content of the plasma in the presence of a tendency to hypercarotenemia in these juvenile diabetic

12. Murrill, W. A.; Horton, P. B.; Leiberman, E., and Newburgh, L. H.: Vitamin A and Carotene: Vitamin A and Carotene Metabolism in Diabetics and Normals, J. Clin. Investigation **20**:395-400 (July) 1941.

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15. Josephs, H. W.: Relation of Vitamin A and Carotene to Serum Lipids, Bull. Johns Hopkins Hosp. **65**:112-124 (July) 1939.

patients bears out the observation of Ralli and associates [10] that lowering of vitamin A is due to slowing of the function of the liver in converting carotene to vitamin A. This statement appears to be contradictory to the conclusions reached in discussion of the results of determination of the plasma carotene. However, from our observation of hypercarotenemia in 28 per cent of these juvenile diabetic patients and of depressed vitamin A levels in 68 per cent (with no excess of vitamin A in the plasma in a single instance), there seems to be evidence of some hindrance in the process of conversion of carotene to vitamin A, though this does not in any way invalidate the hypothesis previously formulated that hypercarotenemia accompanying diabetes depends on the presence of an excess of fat in the blood and in the tissues, which is characteristic of unsatisfactorily controlled diabetes. It may be that fat holds the carotene in solution and prevents its being available for conversion to vitamin A by the liver, an assumption explaining both the tendency to high carotene and low vitamin A levels in the plasma in the present determinations.

Vitamin A–Carotene Ratio.—A large proportion of the vitamin A–carotene ratios for the 114 diabetic children did not fall into the normal range of 0.28 to 0.20. For 67 per cent (76 patients) the ratios were at a level lower than 0.20, which bears out the observations already noted of a high carotene and a low vitamin A level of the plasma and justifies the conclusion previously made that there is some interference in the normal process of conversion of carotene to vitamin A. A ratio above 0.28 in this series was always due to a low carotene level, as is obvious from the fact that none of the vitamin A concentrations were above the normal range. A low carotene intake or a poor absorption of carotene might account for this. On the other hand, the normal or high plasma vitamin A–carotene ratios indicate that utilization of carotene for the formation of vitamin A was normal, or exceeded the normal, in 33 per cent (38) of the patients.

Vitamin B Complex.—Twenty-three patients, or 20 per cent, had signs of vitamin B deficiency. Of these patients, 18 had vitamin B_1 deficiency alone; 2 had deficiency in thiamine and riboflavin, and 3 had ariboflavinosis alone. Of the 10 subjects with clinical vitamin A deficiency, 4 also had deficiency in one of the vitamin B components. Eight (35 per cent) of the vitamin B–deficient group had hepatomegaly, whereas only 12 (13 per cent) of those without vitamin B deficiency had hepatomegaly. Of the vitamin B–deficient group, 27 per cent had histories of uniformly good control of the diabetes; 43 per cent had histories of persistent glycosuria, and 30 per cent had had poorly controlled diabetes, with frequent or recent acidosis. All but 1 of these patients were under treatment with protamine zinc insulin.

The plasma studies of the patients with avitaminosis B revealed carotene and vitamin A levels consistent with the values for the entire group of diabetic patients; a slightly higher percentage of these patients had vitamin C levels below the critical point.

Three subjects with cheilosis on arrival at the camp were observed to have healing or healed lesions after the two week period of dietary supervision and better control of their glycosuria. It was of interest to note that 2 of these children stated that they had noticed "sore corners of the mouth" whenever they overindulged in proscribed foods and that the soreness disappeared when they "behaved."

In the study conducted at the camp in 1941,[1] 24 per cent of the children were found to have vitamin B deficiency. In our experience during two successive summers, 20 to 25 per cent of young diabetic patients proved to have vitamin B deficiency. This figure is somewhat higher than that obtained in other investigations.

Vitamin C.—There were no patients with clinical scurvy, although 5 had positive reactions to tourniquet tests. Four per cent (5 subjects) had a vitamin C level of the plasma below 0.4 mg. per hundred cubic centimeters, that is, the level at which chemical scurvy occurs. None of the children with a positive reaction to the tourniquet test showed plasma values below the critical level. This casts doubt on the validity of the Rumpel-Leede test as a criterion of pronounced vitamin C deficiency. Thirty-nine per cent (43) of the entire 114 diabetic children had vitamin C values for the plasma of 0.8 to 0.4 mg. per hundred cubic centimeters, a level pointing to tissue unsaturation. Our results, showing few instances of vitamin C deficiency, confirm those of other recent studies [16] on this point. It may be concluded that most diabetic children obtain sufficient vitamin C and have adequate utilization of this vitamin.

Relation of Control of Diabetes to Vitamin Status.—There was in our opinion no significant difference in the vitamin A or the vitamin C content of the plasma between the children with consistently satisfactory regulation of their diabetes and those with persistent glycosuria or a history of recurring acidosis. Glycosuria without acidosis and without hypercholesteremia appar-

16. Owens, L. B.; Wright, J., and Brown, E.: Vitamin C Survey in Diabetes, New England J. Med. **224**: 319-323 (Feb. 20) 1941. Sebesta, V.; Smith, R. M.; Fernald, A. T., and Marble, A.: Vitamin C Status of Diabetic Patients, ibid. **220**:56-60 (Jan. 12) 1939.

ently did not cause the carotene level of the plasma to vary remarkably from that for the group as a whole. Among the subjects with recurring acidosis, hypercholesteremia and hepatomegaly a distinct tendency to fewer instances of subnormal levels of carotene in the plasma was apparent; the patients with hepatomegaly, as well as those with hypercholsteremia, included a great number with high values for carotene in the plasma. The possible explanation of this fact has been discussed in the section devoted to carotene. Of the vitamin B-deficient group, 27 per cent had histories of uniformly good control of the diabetes; 43 per cent had histories of persistent glycosuria, and 30 per cent had had poor control of the diabetes, with frequent or recent acidosis. All but 1 of these patients were being treated with protamine zinc insulin. The majority of physicians allow their diabetic patients to exhibit some glycosuria while they are under the influence of protamine zinc insulin; a few countenance a continued high degree of glycosuria. The present observations indicate that avitaminosis B does result when there is persistent glycosuria, even though the diabetic patient is under the influence of protamine zinc insulin.

SUMMARY AND CONCLUSIONS

The results of a study made during the summer of 1942 of the status of vitamins A, B and C in 114 diabetic children at the camp conducted by the New York Diabetes Association were as follows:

Plasma carotene	Percentage	No. of Patients
Hypercarotenemia	28	32
Hypocarotenemia	17	19
Normal	55	63
Plasma vitamin A		
Above normal	0	0
Below normal	68	78
Normal	32	36
Signs of vitamin A deficiency	9	10
Plasma vitamin C		
Tissue saturation (above 0.8 mg. per 100 cc.)	57	65
Tissue unsaturation (between 0.8 and 0.4 mg. per 100 cc)	39	44
Chemical scurvy (less than 0.4 mg. per 100 cc.)	4	5
Positive reaction to tourniquet test	4	5
Signs of the thiamine deficiency	18	20
Signs of riboflavin deficiency	4	5

Hypercarotenemia was observed in 28 per cent of the children. In two comparable series of a decade ago, the incidence of hypercarotenemia was about 85 per cent. The less frequent occurrence of an excess of carotene in the blood is ascribed to the more effective treatment of diabetes which has been developed during the last ten years.

Our results—the direct correlation of the carotene level with the degree of cholesteremia and the parallelism between hepatomegaly and hypercarotenemia—support the concept of the dependence of an increase in carotene on its solubility in fat. This matter will not be completely explained until further concomitant studies of the lipid and carotene contents of the blood of diabetic patients are carried out.

In no instance was the vitamin A content of the plasma above the normal. Sixty-eight per cent of the diabetic children (78) showed a subnormal level of vitamin A.

The notable depression of the vitamin A content of the plasma, in the face of a tendency to hypercarotenemia in these juvenile diabetic subjects, can be accounted for on the basis of an excess of fat holding the carotene in solution and preventing its being available for conversion to vitamin A by the liver.

A study of these patients and of our preceding series (more than 200 children) reveals that 20 to 25 per cent of young diabetic patients treated in the clinics of New York city have vitamin B deficiency.

Hepatomegaly occurred frequently when a vitamin B deficiency existed.

Poor control of the diabetes, as judged by a history of persistent glycosuria, was often accompanied by vitamin B deficiency, even though the subjects had been under the influence of protamine zinc insulin.

The Rumpel-Leede (tourniquet) test did not prove to be valid as a sign of avitaminosis C.

There were no cases of clinical scurvy. Five patients (4 per cent of the series of 114 children) had a vitamin C level of the plasma of less than 0.4 mg. per hundred cubic centimeters, that is, chemical scurvy. Lack of vitamin C is not a problem in diabetes under the management accorded this disease at present.

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EXPERIMENTAL HYPOPROTEINEMIA AND EDEMA

STUDIES OF INTESTINAL ABSORPTION AND INTESTINAL ROENTGENOLOGIC CHARACTERISTICS

ARGYL J. BEAMS, M.D.; ALFRED H. FREE, PH.D., AND JACK R. LEONARDS, PH.D.

CLEVELAND

Comprehensive investigations have been made of the relationship between various deficiency states and the gastrointestinal tract which have resulted in the implication of many deficiencies as causes of disturbed gastrointestinal function. Anorexia, vomiting, diarrhea and other gastrointestinal dysfunctions have been noted in deficiency states,[1] and experimental studies have shown that there are changes in the motility of the stomach and intestine.[2]

The influence of protein deficiency on the gastrointestinal tract has specifically been studied. Barden, Ravdin and Frazier [3] and also Mecray, Barden and Ravdin [4] have shown that the emptying time of the stomach of man and of the dog is noticeably prolonged in the presence of a definite hypoproteinemia, the gastric emptying time varying inversely with the level of plasma proteins. These investigators have also stated the belief that hypoproteinemia may produce so striking an effect on the gastrointestinal tract that severe mechanical defects may be suspected. It has also been demonstrated that hypoproteinemia is associated with a pronounced retardation of the passage of a water-barium sulfate meal through the small intestine of the dog.[5] This decreased motility was accompanied by anatomic changes manifested by bizarre and abnormal roentgenographic patterns of the small intestine. The changes found in hypoproteinemia have been attributed to the edema of the small intestine.

Although these observations may suggest an impairment in intestinal absorption in hypoproteinemia and edema, no direct measurements have as yet been reported. This was the main object of the present study.

METHODS

Adult female mongrel dogs were used in all the experiments. For several weeks before they were used they were fed a stock diet consisting essentially of corn meal and meat supplemented with cod liver oil, yeast and bone meal. Measurements of intestinal absorption of galactose and aminoacetic acid were carried out on all the dogs before the production of edema, and these measurements were compared with those obtained on the same animal in the hypoproteinemic condition. In this manner each animal served as its own control, a procedure which greatly increased the reliability of the results.

Edema was produced in the dogs by reduction of plasma proteins by repeated plasmapheresis. This method was probably first used by Morawitz,[6] and the technic has been adequately described by Holman, Mahoney and Whipple.[7] The dogs were trained to lie quietly on a

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From the Departments of Medicine and Biochemistry, School of Medicine, Western Reserve University, and the University Hospitals.

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(Footnote continued on next page)

"dog board" while blood was being removed and solutions injected. About 40 per cent of the dog's blood volume was removed from the femoral artery or the jugular and femoral veins. Clotting was prevented by the use of sodium citrate. The blood was immediately centrifuged in 100 cc. centrifuge tubes, the plasma drawn off and the cells resuspended in 0.9 per cent solution of sodium chloride. These were then reinjected into one of the veins. When about half of the cells had been returned to the animal, a further 200 cc. of blood was removed. The cells of this blood were kept in the refrigerator and returned to the animal on the next day. This procedure was repeated daily until the plasma proteins were depleted to a suitable level (2 to 3 Gm. per hundred cubic centimeters) and a definite edema could be demonstrated. The absorption and motility studies were then repeated.

The plasma which was removed from 2 of the animals was saved, frozen at 20 F. and stored at that temperature. After the dogs had been rendered hypoproteinemic and the studies in that state were completed, the plasma was warmed to body temperature and the animals were given reinfusions of all or part of their own plasma. Three or four days after return of the plasma, the dogs appeared to be completely recovered, the plasma protein concentration had returned to normal and all traces of edema had disappeared. At this time the roentgenographic and intestinal absorption studies were repeated. Recovery experiments were not done on the other 3 animals. The time which elapsed from the beginning of the depletion period to the completion of the studies after recovery from the hypoproteinemia was about ten days. During this time the animals were fed a low protein diet, consisting of about 200 Gm. daily of a mixture of peeled boiled potatoes and fresh white bread.

Plasma volume and "available (thiocyanate) fluid volume" were determined on 2 of the animals during the control period. These studies were repeated after the dogs had acquired a severe edema and again after the recovery which occurred with plasma transfusion. The methods employed were based on the dilution of the dye T-1824 (plasma volume) and the dilution of thiocyanate (available fluid volume or plasma and interstitial volume) after their intravenous injection. These methods were essentially those described by Gregersen and Stewart [8] as adapted to the use of the Evelyn photoelectric colorimeter.

The methds used to measure the rate of absorption of galactose and aminoacetic acid have already been described in detail.[9] Essentially they depend on the oral administration of the test substance by stomach tube followed by the determination of the concentration of the substance in the blood after definite intervals of time. The type of curve obtained is an indicator of the rate of intestinal absorption. Since the blood concentrations are also affected by the rate of metabolism, this is given consideration in the methods. The metabolism of aminoacetic acid was studied by following the increase in blood urea and urinary excretion of urea. The rate of metabolism of galactose was determined in a separate experiment by the intravenous injection of the sugar over a period of one hour at a constant rate which simulates its rate of entrance into the blood stream from the gastrointestinal tract.

Roentgen studies were carried out on the dogs during the control period after administration by stomach tube of 50 Gm. of barium sulfate suspended in 75 cc. of water. The passage of the barium meal through the gastrointestinal tract was followed fluoroscopically at frequent intervals, and significant changes were recorded by roentgenograms. The studies were repeated at the time the dogs had edema and again when the dogs had recovered from the edema.

RESULTS

The control level of plasma protein averaged 5.4 Gm. per hundred cubic centimeters, whereas the average level of plasma proteins during the period of edema was 2.6 Gm. per hundred cubic centimeters and ranged between 2 and 3.2 Gm. However, at the time many of the tests were being carried out the plasma protein levels of several of the animals were much lower than the values just cited. The average results of studies of galactose absorption are shown in figure 1. It is evident that the blood galactose curves after oral ingestion of the sugar are not significantly different during the time the dogs had edema than during control and recovery periods. The average results of intravenous galactose tolerance studies are shown in figure 2. The curves during control, edema and recovery periods are almost identical in the intravenous studies, indicating that the rates of metabolism are similar. The amounts of galactose excreted in the urine were also similar. In all of the animals there was an insignificant amount of galactose remaining in the stomach one hour after the oral administration of the sugar. This was experimentally ascertained in each of the studies by collection of gastric contents at the end of a one hour period and determination of the galactose content. Since

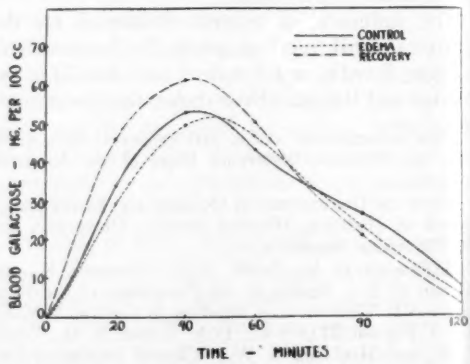

Fig. 1.—Average blood galactose levels following the oral administration of 0.6 Gm. of galactose per kilogram of body weight to dogs before production of edema, during edema and after recovery from edema.

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the rate of metabolism of galactose was not altered by hypoproteinemia, the similarity of the blood galactose curves after oval ingestion is a definite indication that the rate of intestinal absorption was not measurably altered.

The changes in serum amino acid nitrogen and blood urea nitrogen after the oral administration

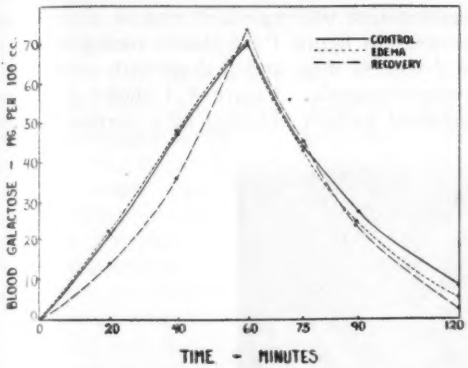

Fig. 2.—Average blood galactose levels following the intravenous administration of 0.6 Gm. of galactose per kilogram of body weight. The sugar was injected at a constant rate during a one hour period. Control values are shown, as well as the curves obtained for the same animals during edema and after recovery.

of aminoacetic acid are shown in figure 3. The average increase in serum amino acid nitrogen was even greater when the dogs were edematous than during the control or recovery period. The increases in blood urea nitrogen were similar during the three periods. The increase in urinary urea nitrogen excretion over the basal level during the six hour period following the oral administration of aminoacetic acid was 100 mg. per kilogram per six hours during the control period and 111 mg. per kilogram per six hours when the dogs were edematous. The similarity of the changes in the blood urea nitrogen and in the urinary excretion of urea nitrogen indicates no significant change in the rate of aminoacetic acid metabolism. The percentage of administered amino acids converted to urea within six hours was calculated according to the method of Kirk.[10] During the control period the animals on the average converted 60 per cent of the aminoacetic acid to urea. This amount increased to 85 per cent when the dogs were edematous, and during the recovery period it was 53 per cent. As has already been pointed out,[9a] with this dose from 39 to 75 per cent of the aminoacetic acid is usually converted to urea in normal dogs. This is a further indication that the hypoproteinemic dogs are metabolizing the acid in a manner and at a rate similar to the normal. These results may be interpreted as indicating that the rate of intestinal absorption of aminoacetic acid was not decreased in the presence of edema.

The results of the measurements of plasma volume and available (thiocyanate) fluid volume are given in the table. It can be seen that plasma volumes were not significantly altered by the experimental procedures. The measurements of the available (thiocyanate) fluid volume show a pronounced increase as a result of production of hypoproteinemia and edema. These figures particularly emphasize that a massive edema was produced in these animals. The available (thiocyanate) fluid volume increased over 20 per cent of the body weight, which was consistent with the edema observed clinically. On restoration of normal plasma protein levels an extensive diuresis occurred, which eliminated the edema and brought the available (thiocyanate) fluid volume back to normal levels.

Plasma and Available (Thiocyanate) Fluid Volumes in Hypoproteinemia and Edema

Dog No.	Condition	Weight, Kg.	Plasma Volume, Cc.	Available (Thiocyanate) Volume, Cc.	Plasma Protein, Gm. per 100 Cc.
89	Control	13.5	600	3900	5.3
	Edema	14.5	615	7200	1.9
	Recovery	11.5	670	3600	5.3
92	Control	14.5	700	4700	4.5
	Edema	17.6	720	7400	2.0
	Recovery	13.0	700	4000	6.0

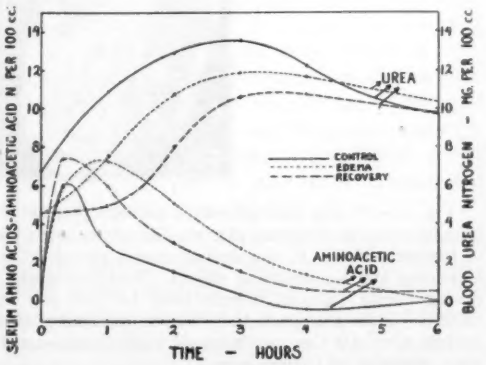

Fig. 3.—Average increases in serum amino acid nitrogen and changes in blood urea nitrogen following the oral administration of 0.6 Gm. of aminoacetic acid per kilogram of body weight. Curves are shown for control dogs, edematous animals and dogs after recovery.

In the 2 animals in which reinfusion of plasma was carried out, the urea excretion during and after the infusion of plasma was studied. A total of 3,050 cc. of plasma, containing 81 Gm. of protein, was removed from dog 89 during the depletion period. Of this amount, 2,050 cc., con-

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taining 55 Gm. of protein, was reinjected intravenously at a constant rate over a twelve hour period. This restored the plasma protein from 2.36 Gm. per hundred cubic centimeters to the original normal level, of 5.3 Gm. per hundred cubic centimeters. The amount of plasma removed from dog 92 totaled 2,500 cc. and contained 71 Gm of protein. This was all returned to the animal over a twenty hour period and elevated the plasma protein from 1.97 Gm. to 6 Gm. per hundred cubic centimeters, the latter value being even higher than the original control level of plasma protein. The excretion of urea was determined for the dogs before and after the injections of plasma. The increase in urea excretion was not striking and indicated that most of the plasma protein that was injected was retained, less than 15 per cent of the administered protein being converted to urea during the first forty-eight hours, at which time the rate of urea excretion had returned to the original basal level.

There were no striking differences in the appearances of the intestinal pattern of the edematous animals as compared with their control roentgenographic studies. In some of the roentgenograms of the small intestines during edema there was clumping of the barium and segmentation. The significance of this observation is questionable, since these abnormal patterns were noted in some of the roentgenograms obtained from the control group. Whenever clumping and segmentation was noted, it was of a moderate nature. In figure 4 are shown roentgenograms of 2 control dogs and 2 dogs with edema and hypoproteinemia. Figure 4 *A* shows a normal intestinal pattern obtained in a normal control animal, while figure 4 *B* shows clumping and segmentation in a normal control animal. Figure 4 *C* illustrates a normal intestinal pattern obtained in a dog with hypoproteinemia and edema, while figure 4 *D* shows clumping and segmentation in an edematous animal.

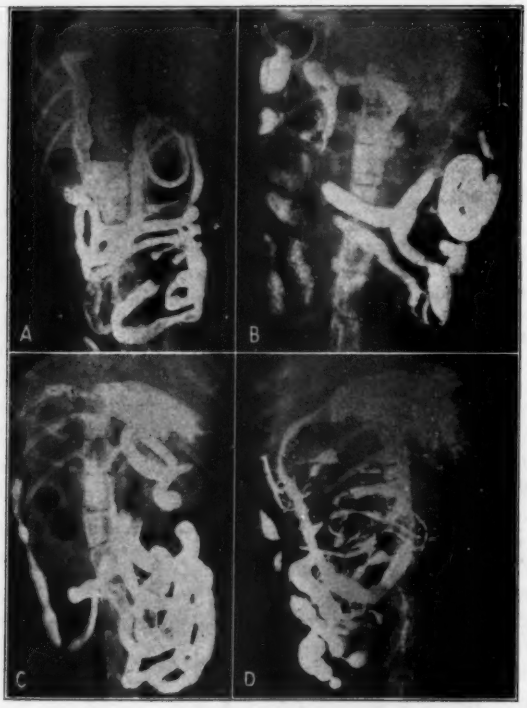

Fig. 4.—*A*, dog during control period (plasma protein level 5.3 Gm. per hundred cubic centimeters). No changes noted in intestinal pattern. Roentgenogram taken three hours after oral ingestion of aqueous suspension of barium sulfate. *B*, dog during control period (plasma protein level 5.6 Gm. per hundred cubic centimeters). Clumping and segmentation shown. Roentgenogram taken three hours after ingestion of barium sulfate. *C*, dog during edema (plasma protein level 1.6 Gm. per hundred cubic centimeters). No changes noted in intestinal pattern. Roentgenogram taken thirty minutes after ingestion of barium sulfate. *D*, dog during edema (plasma protein level 1.9 Gm. per hundred cubic centimeters). Clumping and segmentation shown. Taken thirty minutes after ingestion of barium sulfate.

Studies of intestinal motility made during the control period were compared with comparable studies on the edematous hypoproteinemic animals. In no instance was the initial emptying

of the stomach delayed during hypoproteinemia. Furthermore, the time required for complete evacuation of the barium meal from the stomach was approximately the same during edema as during the control period or during the recovery period. Observations regarding the speed with which the barium sulfate moved along the intestine indicated that the intestinal motility of the animals was not decreased by hypoproteinemia and edema.

COMMENT

Since our experiments have shown no changes in gastrointestinal motility or in absorption rates following the production of hypoproteinemia and edema and only slight changes of the intestinal roentgenographic patterns, it should be emphasized that the animals in the present study had lower plasma protein levels and probably more edema than were attained by other investigators who have studied the same phenomena.[11] We have established this fact by numerous observations, which include: multiple measurements of plasma protein levels; clinical observations of edema and ascites; gross observations of the visceral edema of 1 of the dogs killed at a time when the plasma proteins were at a low level; pronounced increases in weight and available (thiocyanate) fluid volume, and the production of pronounced diuresis on restoration of the plasma protein concentration to normal values. In the animal which was killed the edema of the visceral organs was even more pronounced than that observed in the skin and extremities. Both the pleural and peritoneal cavities contained considerable free fluid, and all of the abdominal viscera showed clearcut evidences of edema. It should be noted that the critical level of plasma protein concentration at which edema appears in the dog is considerably lower than that at which edema usually appears in human beings with hypoproteinemia.[12] In the present experiments no gross manifestations of edema were noted in any of the dogs as long as the plasma protein concentration was above 3 Gm. per hundred cubic centimeters. In the report of Barden, Thompson, Ravdin and Frank [5] no specific mention is made as to whether or not their animals had any demonstrable edema, although they assumed that edema of the intestinal wall accounted for the phenomena noted. From the data presented by these investigators it would appear that the plasma protein levels of their animals ranged between 3.2 and 4.5 Gm. per hundred cubic centimeters.

The roentgenologic methods used for the estimation of gastric emptying time are difficult to evaluate even when employed by skilled operators. In our experiments the presence of hypoproteinemia and edema had little effect on gastric emptying time and on motility of the small intestine. The absence of any decrease in gastric emptying time is adequately confirmed by the normal galactose tolerance curves. We have repeatedly observed by analyses of the gastric residuum that orally administered galactose in doses of 0.6 Gm. per kilogram is almost completely emptied in forty-five minutes. The average maximum blood galactose level occurred at forty minutes in both normal and hypoproteinemic states. This offers good evidence to substantiate the occurrence of normal gastric emptying during hypoproteinemia and edema. The roentgen studies on the dogs also indicated that gastric emptying time and intestinal motility were not decreased during edema. These results are not in agreement with those of Barden, Thompson, Ravdin and Frank,[5] who found striking increases in gastric emptying time and decreases in small intestinal motility in dogs kept on a low protein diet for prolonged periods of time. There may have been several factors which could account for the discrepancies. The most evident difference in the two studies is that whereas edema was rapidly produced in our experiments with a minimum change in the condition of the animals other than the lowered plasma protein level, in the experiments of Barden and associates the hypoproteinemia was produced by dietary means. The diet and nutritional condition of the animals may have accounted for the changes in gastrointestinal motility to which hypoproteinemia per se may have contributed only an insignificant amount.

In sprue there is a pronounced impairment in intestinal absorption and there is also a significant change in the intestinal roentgen pattern.[13] This may suggest that there is a correlation between impaired intestinal absorption and abnormal roentgenographic observations, and many authors have spoken of this possibility. In certain conditions other than sprue evidence of impaired

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absorption and abnormal roentgen patterns are obtained simultaneously.[14] In the case of clinical hypoproteinemia and edema most current opinion seems to favor the idea that there is an abnormal roentgen pattern in the intestine, although there have been no extensive clinical reports published on this subject. This is hard to understand, since there is a great abundance of clinical material available and it has been seven years since Pendergrass and associates [15] called attention to this possibility as a result of observations on 1 subject. From a clinical standpoint there is no evidence to suggest that in edema there is a significant impairment in intestinal absorption as evidenced by large amounts of fat and nitrogen in the stool. The present studies demonstrate experimentally that intestinal absorption is not appreciably affected by hypoproteinemia and edema.

The plasma volume in edema has been studied by many different technics with rather discordant results. Harris and Gibson [16] have reviewed the results of many of these studies and have reported plasma volume values in a series of patients with edema, the plasma volume being determined by the injection of the dye T-1824. These investigators noted that in edema the average plasma volume is slightly increased above the normal average. The present observations indicate that in edema due to hypoproteinemia there is no significant change in plasma volume as measured by the dilution of the dye T-1824 but that there is a great increase in interstitial fluid volume as measured by the dilution of intravenously injected thiocyanate.

The results of the nitrogen balance studies carried out after restoration of plasma protein are in agreement with the observations of Elman and Davey,[17] who noted that there is a tenacious retention of protein nitrogen when administered intravenously to hypoproteinemic subjects.

Recent observations have indicated that impaired hepatic function may be associated with nutritional hypoproteinemia in dogs [18] and hypoproteinemia due to nephrosis in children.[19] The evidence for impaired hepatic function was obtained by retention of plasma amino acid following injection of casein hydrolysate. In our experiments, although there appeared to be a small retention of plasma amino acids following ingestion of aminoacetic acid in the hypoproteinemic dogs, there were no changes in the increase in concentration of urea in the blood or in urinary excretion of urea. The curves after the intravenous administration of galactose were also normal and indicated no impairment of hepatic function in our animals.

SUMMARY AND CONCLUSIONS

Hypoproteinemia with edema was produced in 5 dogs by means of plasmapheresis.

The intestinal absorption of galactose and aminoacetic acid was studied by means of improved tolerance tests. The presence of hypoproteinemia and edema had no significant effect on the rate of intestinal absorption of galactose and aminoacetic acid.

Roentgenologic observations of the gastrointestinal tract were made after the oral administration of barium sulfate. Gastric emptying and intestinal motility were not altered by hypoproteinemia and edema. In some of the roentgenograms of the small intestine during edema there was moderate clumping of the barium and segmentation. These phenomena were also noted in the studies on normal animals, although they occurred less frequently.

Studies of plasma volume and available (thiocyanate) fluid volume indicated that during edema the plasma volume is not significantly altered but that the available (thiocyanate) fluid volume is noticeably increased.

The rate of metabolism of galactose and aminoacetic acid was not altered by hypoproteinemia and edema.

The members of the roentgenologic department of University Hospitals cooperated in these studies, and Mrs. Annabelle Miller gave technical assistance.

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BRONCHOSPASM ASSOCIATED WITH PULMONARY EMBOLISM

RESPIRATORY FAILURE

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Increasing awareness of the importance of pulmonary embolism is becoming apparent in the thinking of surgeons and internists alike. Many aspects of the problem have been studied in the laboratory and at the bedside; yet there is still much to be learned concerning both the prophylaxis and the management of this important and extremely common complication in medical, surgical and obstetric patients.

The possibility that bronchospasm may be associated with pulmonary embolism, with material increase in respiratory distress and anoxemia, has been suggested by several investigators. In 1920 Dunn [1] described histologic changes in embolized lungs consisting of spasm of the musculature of the bronchiolar terminations and of the atria, but not of the bronchioles themselves. In 1924, however, Binger, Brow and Branch [2] observed similar changes in normal, nonembolized lungs. Singh,[3] using an oncometer to measure changes in the lung volume of decapitated cats, reported that air embolism produced bronchospasm which could not be prevented by atropine, but which could be abolished by epinephrine. His explanation of the reflex mechanisms involved in decapitated animals is cumbersome and inadequate. His deduction that the effects of epinephrine were exerted on the airways, rather than on the pulmonary circulation, are unconvincing in view of the unreliability of the oncometric method when used with organs containing both blood and gases.

Binet and Burstein [4] produced embolization of the lungs of dogs by the intravenous injection of lycopodium in oil and, employing a modification of Jackson's [5] method for the registration of bronchial reactions, were able to show bronchoconstriction which could be abolished by atropine or by vagotomy. Judging from their published records, which showed a precipitous fall in blood pressure without recovery, one may conclude that the animals had been subjected to rapidly fatal massive embolization. The practical importance of bronchospasm under such conditions is open to question.

Jesser and de Takáts,[6] in an investigation of the roentgenographic pattern of the bronchial tree after injection of chloriodized peanut oil, reported changes in the pattern following pulmonary embolism which they interpreted to mean constriction of the bronchi. They stated that roentgenograms of the normal bronchial tree of the dog showed that only the large bronchial radicles filled with radiopaque material, and that after pulmonary embolism the smaller radicles became filled. It was evidently their opinion that contraction of the large bronchi had forced the contrast medium into the fine radicles. It is probable that if any reflex bronchospasm occurred it would be most evident in the more muscular bronchioles, filling of which would be more, rather than less, difficult. One might, therefore, be justified in interpreting their results as indicating dilation of the small bronchi and bronchioles. They stated the belief that they had eliminated increased respiratory effort as the cause of the change in bronchial pattern by showing that no change appeared in the normal bronchogram when violent respiratory efforts were induced by clamping the trachea. This method did not conclusively demonstrate the point, for it eliminated the distending and displacing force of the inrushing air.

Because of certain objections to some of the methods employed, as well as the possible importance of such bronchial reactions if they do occur, it seemed desirable to reexplore the problem.

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6. Jesser, J. H., and de Takáts, G.: The Bronchial Factor in Pulmonary Embolism, Surgery **12**:541, 1942.

METHODS

Two methods for the recording of bronchial reactions were used in the present study. The first method consisted in rhythmic inflation of the lungs of anesthetized dogs with a force pump which delivered a constant volume of air into the trachea at a constant rate, variations in intratracheal pressure being recorded at the same time. It was assumed that a change in resistance to the flow of air brought about by changes in the caliber of the bronchial tree would be reflected by corresponding changes in intratracheal pressure. In order to eliminate the effects of the animal's own respiratory efforts, which may become violent after embolism, it was necessary to open the chest widely. This was accomplished by splitting the sternum and retracting its edges. The need for deep anesthesia and extensive operative procedures introduces serious objection to the method.

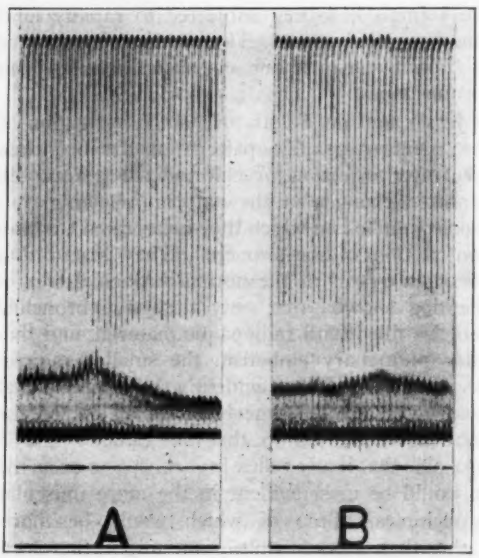

Fig. 1.—Tests of the validity of one of the methods used to record bronchial reactions. The animal was receiving artificial respiration, the lungs being inflated by a pump which delivered a constant volume of air at a constant rate. Any change in intratracheal pressure (upper curve) indicates a change in the resistance to the flow of air into the lung. *A* shows the effects of intravenous injection of 0.2 mg. of histamine phosphate on the intratracheal pressure and the pressure in the right ventricle (lower curve). Downward deflection indicates increased intratracheal pressure. *B* shows the effects of clamping the hilus of one lobe of the lung. The time interval equals one second.

The second method consisted of simultaneous registration of intratracheal and intrapleural pressures in normally breathing, lightly anesthetized dogs. It was assumed that if the intratracheal and the intrapleural pressure changed in opposite directions, a change in the patency of the bronchial tree had occurred. The principle is essentially that involved in Jackson's method except that in the latter the changes in intrapleural pressure are kept constant by means of a rhythmic suction pump. Thus, if intratracheal pressure decreased while intrapleural pressure increased, it was assumed that bronchoconstriction had occurred. We also accepted as indicating bronchoconstriction records which showed no change in intratracheal pressure despite significant increases in intrapleural pressure. We have been unwilling to accept as evidence of bronchoconstriction records in which both intrapleural and intratracheal pressure increased, even though the increase in the intrapleural pressure was disproportionately greater than the increase in intratracheal pressure. It is possible that such changes are valid evidence of bronchoconstriction, but we have been reluctant to accept them as such.

The results of procedures designed to test the validity of the methods are shown in figures 1 and 2. Figure 1 *A* shows the effect of intravenous injection of 0.2 mg. of histamine phosphate on the intratracheal pressure (upper curve) and the pressure in the right ventricle (lower curve) in an animal prepared by the first method. The maximum intratracheal pressure which developed during the "inspiratory" phase (downward deflection) was increased definitely but not conspicuously. Indeed, the degree of change was surprisingly small in view of the fact that direct observation of the lungs revealed little, if any, inflation. Figure 1 *B* illustrates the effects of clamping the hilus of the upper lobe of the right lung. The increase in intratracheal pressure was again definite but not pronounced.

The tests seemed to indicate that the method was valid for demonstration of high degrees of bronchoconstriction but that it was probably not sensitive to less intense bronchial reactions.

Figure 2 shows the effect of injection of 0.5 mg. of acetylbetamethylcholine chloride on intratracheal pressure (upper curve) and intrapleural pressure (lower curve) in the normally breathing animal (method 2). It will be noted that, despite a notable increase in intrapleural pressure, little, or no, variation in pressure occurred in the trachea until the effects of the drug began to wear off. Although this method proved to be more sensitive than method 1, it has certain limitations, the most important of which is the difficulty in evaluation of differential changes in the intratracheal and intrapleural pressures during changes in the respiratory rate and the duration of the respiratory phases. In the evaluation of experimental results this factor must be given due consideration.

PROCEDURE

Mongrel dogs, weighing 6 to 10 Kg., were anesthetized with sodium pentobarbital (40 mg. per kilogram of body weight in experiments with method 1 and 20 to 25 mg. per kilogram of body weight in experiments with method 2). When measurements of pressure in the right ventricle were made, the animal's blood was rendered noncoagulable by the use of heparin (1 mg. per kilogram of body weight) and calcomine fast pink[7] (120 mg. per kilogram of body weight).

Large pulmonary emboli were produced by the intravenous injection of a suspension of barium sulfate[8] or by introduction into the venous circulation of thin sheet rubber cut into strips 15 cm. long and 1.5 mm. wide. The method of introduction of the rubber strips was as follows: The external jugular vein was cannulated with a glass tube having an inner diameter of 2 mm. and sufficient length to allow its passage into the superior vena cava. Rubber emboli were then fitted into a number of similar glass tubes, and the tubes filled with

7. This substance was furnished by Calco Chemical Company, Bound Brook, N. J.

8. de Takáts, G.; Beck, W. C., and Fenn, G. K.: Pulmonary Embolism, Surgery **6**:339, 1939.

isotonic solution of sodium chloride. A tube containing an embolus was connected to the cannula by means of rubber tubing and the embolus forced into the vena cava by the injection of isotonic solution of sodium chloride from a syringe. These emboli were soft and pliable, passed readily through the chambers of the heart and, after blocking some of the larger branches of the pulmonary artery, accumulated in the main pulmonary artery to form a rider embolus, as shown in the accompanying sketch (fig. 3). This proved to be a simple and effective method for the repeated introduction of two emboli had no apparent effect on intratracheal pressure, this result indicating that the presence of the foreign bodies in the pulmonary arteries did not produce demonstrable reflex effects on the bronchi, nor was the resistance in the pulmonary circuit sufficiently increased to be reflected in changes in pressure in the right ventricle. A few seconds before the introduction of the fourth embolus the pressure in the right

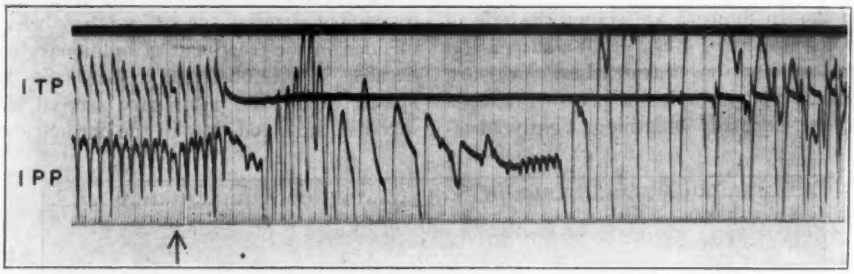

Fig. 2.—Effects of intravenous injection of 0.5 mg. of acetylbetamethylcholine chloride (mecholyl chloride) on the intratracheal pressure (*ITP*) and the intrapleural pressure (*IPP*) in a normally breathing, lightly anesthetized dog. Bronchoconstriction is indicated by a decrease in the intratracheal pressure despite a conspicuous increase in the intrapleural pressure. Time intervals, four-hundredths and two-tenths seconds.

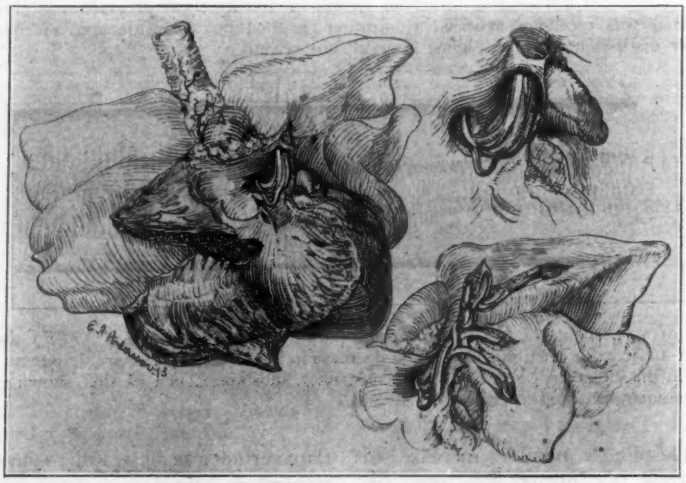

Fig. 3.—Drawing of the pulmonary arteries filled with rubber emboli. For description see text.

moderate-sized emboli, and, by injection of the rubber strips in rapid succession, massive embolism of the main pulmonary artery was produced. From eight to twelve such emboli were sufficient to block effectively the pulmonary circulation and to cause the death of the animal.

RESULTS

Method 1.—Figure 4 shows the effects of repeated introduction of rubber strips into the pulmonary circulation on the intratracheal pressure (upper curve) and the right ventricle (lower curve). It will be noted that the first intraventricle gradually rose, and, simultaneously, there was an increase in the maximum intratracheal pressure (downward deflection), a phenomenon which we interpret to indicate bronchoconstriction. It will be noted that the latter effect disappeared toward the end of the recording, even though the intraventricular pressure remained elevated. Although the increase in the recorded amplitude of intratracheal pressure was not striking, it represented almost as great a percentile increase as that produced by

the intense bronchoconstriction induced by histamine, shown in figure 1.

In only 3 of 10 experiments with this method were effects produced comparable to those illustrated in figure 4. In 2 other experiments there was suggestive, but unreliable, evidence of slight bronchoconstriction. It was because of the inconsistency of results, together with the evident lack of sensitivity of the method, that we turned to the second method.

Method 2.—In figure 5 are shown the effects of an embolus consisting of 0.5 cc. of a suspension of barium sulfate on intratracheal pressure (upper curve) and intrapleural pressure (lower curve) in the normally breathing, lightly anesthetized dog. Despite a notable increase in intrapleural pressure, the intratracheal pressure was temporarily much diminished, although the changes were less than those produced by mecholyl chloride, as illustrated in figure 2. The bronchospasm was apparently transitory, but if we were to accept disproportionate increases in intratracheal and intrapleural pressures as indicative of bronchial reactions, the effect would be somewhat more sustained.

Changes similar to those already described were encountered in 5 of 7 animals with which this method was used. Thus, the percentage of positive results was considerably greater with method 2 than with method 1.

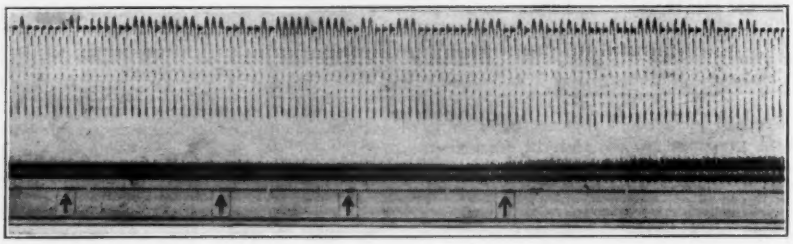

Fig. 4.—Effects of repeated introduction of rubber emboli on intratracheal pressure and pressure in the right ventricle. The animal was receiving artificial respiration (method 1). The injections of emboli are marked by arrows. For further discussion see text. Time interval, one second.

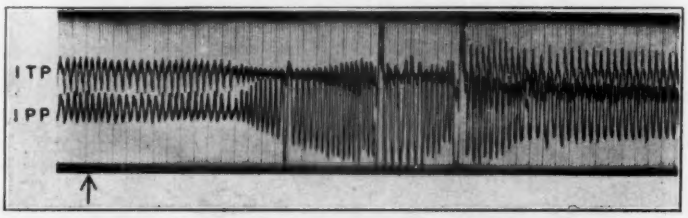

Fig. 5.—Effects of an embolus of 0.5 cc. of barium sulfate on the intratracheal (*ITP*) and the intrapleural (*IPP*) pressure in a normally breathing dog. The decrease in intratracheal pressure despite an increase in pleural pressure is similar to the effect of a known bronchoconstrictor substance, such as that shown in figure 2. Time is expressed in four-hundredths and in two-tenths second.

EFFECT OF DRUGS AND VAGOTOMY

Because bronchoconstriction associated with pulmonary embolism was transient as measured by the methods used, it was necessary to inject a drug or sever the cervical vagus nerves before the introduction of emboli and to evaluate the effectiveness of such procedures in the prevention of bronchoconstriction, rather than in the treatment of constriction after it had occurred.

Papaverine.—Papaverine has been widely used to combat arterial spasm and has been recommended in the treatment of pulmonary embolism because it was observed to overcome bronchospasm,[6] dilate the pulmonary arterial tree [8] and increase the blood flow in the coronary arteries.[9] Papaverine was observed to quiet the increased respiratory efforts associated with experimental pulmonary embolism following a temporary phase of stimulation of respiration.[10]

We have also observed brief stimulation of respiration, lasting ten to thirty seconds, pro-

9. Essex, H. E.; Wegria, R.; Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, Am. Heart J. **19**:554, 1940. Lindner, E., and Katz, L. N.: Further Observations on the Action of Drugs on the Caliber of Coronary Vessels, J. Pharmacol. & Exper. Therap. **72**:306, 1941.

10. Megibow, R. S.; Katz, L. N., and Feinstein, M.: Kinetics of Respiration in Experimental Pulmonary Embolism, Arch. Int. Med. **71**:536 (April) 1943.

duced by papaverine. After this transient stimulation respirations became quieter, and the animal seemed to be somewhat protected against the lethal effects of embolization.

Records of the bronchial reactions, however, proved somewhat surprising, for there regularly appeared evidence of transient bronchoconstriction which was not followed by demonstrable bronchodilation. The temporary increase in resistance to the flow of air into the lungs appeared at the time of, and persisted for as long as, the initial stimulation of respiration. The drug usually produced a fall in pressure in the right ventricle, but in 1 experiment a rise was observed; bronchoconstriction occurred independently of changes in the intraventricular pressure, as shown in figure 6.

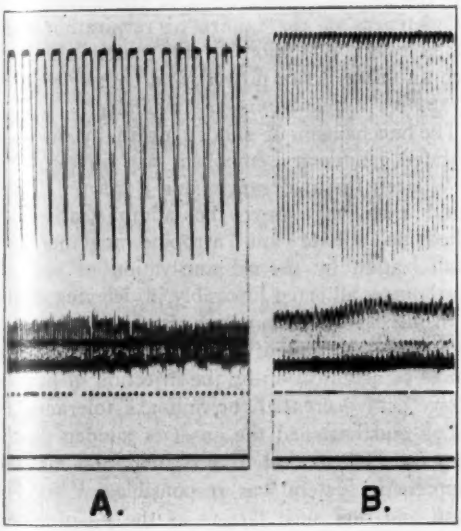

Fig. 6.—Effects of papaverine on intratracheal pressure and pressure in the ventricle in dogs receiving artificial respiration. There was a brief increase in resistance to the flow of air into the lungs, as indicated by a higher maximal intratracheal pressure (downward deflection). For further discussion see text.

Atropine and Cervical Vagotomy.—Four animals were subjected to pulmonary embolization after atropinization (1 to 2 mg. of atropine sulfate intravenously) or cervical vagotomy. None showed evidence of bronchoconstriction. The number is too small to permit more than the tentative conclusion that the reflex is mediated over the vagus nerve.

Digitalis.—It has been suggested by Jesser and de Takáts [6] that drugs which increase vagal tone, such as digitalis, increase the degree of bronchoconstriction associated with pulmonary embolism and are therefore contraindicated. We were unable to detect any clear evidence of increased bronchospasm following the intravenous administration of 0.4 mg. of lanatoside C [11] in 4 embolized dogs.

COMMENT

The transient nature of the bronchoconstriction which appeared after pulmonary embolism raises doubt concerning its practical importance. Further doubt is cast by the observation of Megibow, Katz and Feinstein [10] that in the early stages of experimental pulmonary embolism the oxygen content of arterial blood was increased and the carbon dioxide content decreased. Their observations seem hardly consistent with the production of intense and sustained bronchospasm. It is possible that in unanesthetized human beings bronchoconstriction might be more sustained than in the experimental animal, although we have never encountered clinical evidence in the form of asthmatic breathing in patients with normal hearts. In persons with underlying heart disease, however, pulmonary embolism may precipitate acute heart failure, with cardiac "asthma."

Since atropine has appeared useful, on empiric grounds, in the treatment of pulmonary embolism,[8] and since it may be expected to counteract any bronchospasm which may be present, its use is recommended even though the clinical importance of bronchoconstriction remains in doubt. Epinephrine should not be used for the control of possible bronchospasm associated with pulmonary embolism because of the observation (our own and others [6]) that under such conditions intense pulmonary edema often follows. The demonstration that papaverine appears to produce brief bronchoconstriction should not be a bar to its use, in view of its apparently beneficial effects on other structures.

Megibow, Katz and Feinstein [4,10] reported evidence that the accelerated respiration following pulmonary embolism was dependent on a rise in pressure in the pulmonary artery, the right chambers of the heart and the superior vena cava. Our observations suggest that the reflex producing bronchospasm may have the same cause, for in experiments in which the pressure in the right ventricle was measured we did not observe bronchoconstriction in the absence of a rise in pressure in the right ventricle. Disappearance of bronchoconstriction, after an interval of one or two minutes, even though intraventricular pressure remained elevated, suggests—aside from the possibility that some factor other than the rise in pressure provided the stimulus for the reflex—that compensatory or antagonistic mechanisms

11. This substance was furnished by the Sandoz Chemical Works, Inc., New York.

were set into action or that fatigue and adaptation occurred in the reflex arc.

Respiratory Failure.—So much attention has been given to the heart and circulation in both clinical and experimental pulmonary embolism that it seems desirable to direct attention to the observation that death from pulmonary embolism in the spontaneously breathing experimental animal was generally due to respiratory, and not to cardiac, failure. In most experiments the heart continued to beat regularly for thirty to ninety seconds after respiration had ceased.

While these observations indicate that death was due principally to respiratory failure, it does not necessarily follow that circulatory changes did not play an important role. Respiratory failure is usually to be attributed to depression of the respiratory center by drugs, such as opiates or barbiturates, or to anoxia of the center. Anoxia of the center may be brought about by low oxygen saturation of arterial blood or by a reduction in blood flow. The reduction in blood flow, in turn, may be due to a decrease in systemic arterial pressure or to an increase in venous (or intracranial) pressure or to both. It is evident that under the conditions of our experiments on barbitalized dogs, and, to a large extent, in human beings, all of these factors may be present in varying degrees. In the later stages of pulmonary embolism anoxemia frequently occurs, and at the same time there may be a fall in arterial and a rise in venous pressure. Thus the circulatory effects of pulmonary embolism may be important contributory, or even primary, factors in failure of respiration.

Two types of respiratory failure were seen. The more common one was characterized by periodic breathing of the Cheyne-Stokes form, followed by gradual cessation of breathing, with the usual final slow, gasping efforts. This type of failure followed a prolonged period of rapid, labored breathing, and it is probable that the increased activity of the center hastened its exhaustion. Oxygen therapy not only combats anoxemia, but, by so doing, reduces the respiratory rate,[12] and hence the metabolism of the respiratory center. Thus, not only the oxygen supply to the center is increased, but, at the same time, its oxygen requirement is diminished. Papaverine was the only drug of a number tried by Megibow, Katz and Feinstein [10] that had any significant effect in reducing the accelerated respiratory rate associated with experimental pulmonary embolism. This drug can, therefore, be considered useful, if only for the purpose of diminishing the metabolic activity of the center. It is probable, however, that its more important action is in removing the underlying causes of the original acceleration. Thus these two agents (oxygen and papaverine) may be expected to stave off exhaustion of the respiratory center. Depression of the center by injudicious use of opiates or barbiturates is of course to be avoided.

The second type of respiratory failure was observed in animals which were subjected to repeated introduction of emboli while they were in respiratory distress from previous embolization. This type of respiratory failure was sudden, and so complete that even the terminal gasping, usually a hardy respiratory function, was completely abolished. The suddenness and completeness of the failure of respiration suggested reflex inhibition of the center, although such an effect is not proved, and equally tenable alternative explanations are available.

The mechanism of sudden death in cases of repeated pulmonary embolism was investigated by Villaret, Justin-Besançon and Bardin.[13] They found that vagotomy, the administration of ephedrine sulfate and atropine together, or alkalinization by the administration of sodium bicarbonate, all acted favorably in delaying death or in increasing the number of emboli tolerated. Conversely, section of the cervical sympathetic nerves or acidification by the injection of hydrochloric acid decreased the animal's tolerance to emboli and hastened the onset of sudden death. They concluded that reflex inhibition of the sympathetic system was responsible for sudden death and that such factors as the p_H of blood or tissues may be modifying factors. Their experimental results, however, do not exclude alternative mechanisms. For example, vagotomy slows the rate of discharge of the respiratory center in normal animals and, to a less extent, in animals with pulmonary embolism. If the oxygen requirements of the center are thus reduced its eventual deterioration may be postponed. The efficacy of ephedrine may have depended largely on its ability to raise arterial pressure so that blood flow to the center was increased, and hence its oxygen supply improved. Whatever the mechanism of sudden death may be, these experimental results indicate that it can be favorably influenced by drugs.

12. Binger, C. A. L.; Brow, G. R., and Branch, A.: Experimental Studies on Rapid Breathing: II. Tachypnea, Dependent upon Anoxemia, Resulting from Multiple Emboli in the Larger Branches of the Pulmonary Artery, J. Clin. Investigation **1**:155, 1924-1925.

13. Villaret, M.; Justin-Besançon, L., and Bardin, P.: Physio-pathologie des accidents mortels consécutifs aux embolies pulmonaires, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:936, 1936; Recherches sur la prévention expérimentales des accidents consécutifs aux embolies pulmonaires, ibid. **52**:941, 1936.

The treatment of pulmonary embolism resolves itself into maintenance of an adequate oxygen supply to the heart muscle and to the respiratory center. When there is arterial anoxemia, much can be expected from oxygen therapy, but alone it may be insufficient. A pressor drug, such as epinephrine, might be expected to improve the blood supply to the heart and to the medulla, but use of this drug may be unsuitable under the circumstances. Its tendency to produce pulmonary edema has been mentioned. In addition, epinephrine increases general metabolism, increases the work of the heart and produces an increase in venous pressure. Ephedrine, on the other hand, produces a greater and more sustained rise in blood pressure; at the same time, it does not increase the metabolic rate and cardiac work to as great an extent as does epinephrine.[14] There is, therefore, both theoretic and experimental evidence to indicate that ephedrine may be useful in combating respiratory failure in cases of pulmonary embolism. Some of the newer pressor drugs, such as paredrine (p-hydroxy-*a*-methylphenylethylamine hydrobromide) or paredrinol (p-hydroxyphenylisopropylmethylamine sulfate), may prove even more suitable.

CONCLUSIONS

Dogs subjected to pulmonary embolism showed transient bronchoconstriction.

The available evidence indicates that bronchoconstriction is a reflex mediated over the vagus nerves and that the afferent impulses are dependent on a rise in pressure in the right chambers of the heart.

Drug therapy may have certain applications, although the clinical importance of the bronchospasm is still open to question. Atropine apparently prevents bronchospasm, while papaverine produces transitory constriction. Both drugs have been found useful in the treatment of pulmonary embolism and should be used. Digitalis in the form and dosage used has no appreciable effect on the bronchi. It can, and should, be used when there is auricular fibrillation or congestive heart failure without fear of possible harmful effects on the bronchi. Epinephrine should not be used as a bronchial antispasmodic because of the ready production of pulmonary edema following its administration.

The death of our experimental animals was usually due to respiratory failure. Failure of the respiratory center is complex and inextricably bound up with failure of the circulation. Therapeutic agents most likely to support both the circulation and the respiratory center appear to be (1) oxygen, (2) papaverine and (3) drugs capable of raising the systemic blood pressure without producing undesirable side effects. Ephedrine fulfils the last requirements reasonably well.

This work was done with the technical assistance of Miss Alice M. Lennon.

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Massachusetts Memorial Hospitals.

14. Starr, I.; Gamble, C. J.; Margolies, A.; Donal, J. S., Jr.; Joseph, N., and Eagle, E.: Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size; on Respiration, on Metabolic Rate and on the Electrocardiogram, J. Clin. Investigation **16**:799, 1937.

URINARY EXCRETION OF NICOTINIC ACID AND ITS DERIVATIVES

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Numerous studies have been made of the excretion of nicotinic acid and its derivatives in the urine, but as yet no satisfactory test has been devised for evaluation of the nutritional status of a person with regard to nicotinic acid. Deficiency is diagnosed on the basis of clinical findings. In view of the importance of nicotinamide in intermediary metabolism, a procedure is needed which will detect mild states of deficiency and indicate the degree of depletion in the tissues. Valuable contributions toward this end have been made by many investigators, including Melnick, Field and their collaborators [1] and Perlzweig and his co-workers.[2] Recently, Perlzweig, Sarett and Margolis [3] suggested that the urinary excretion following the administration of 500 mg. of nicotinamide may serve as a test of nutritional condition in relation to nicotinic acid.

The object of this investigation was to study further the urinary excretion of nicotinic acid and its derivatives and, if possible, to devise a test which would assist in estimating the adequacy or deficiency of the supply of this vitamin in the human subject. Some of the findings were reported in a preliminary note.[4] Observations were made for 13 normal persons, 24 hospitalized patients with various acute and chronic diseases and 26 patients with clinical evidence of deficiency of one or more members of the B group of vitamins. Thirteen of the patients in this last group had typical pellagra, 10 had symptoms of nicotinic acid deficiency without dermatitis, 2 had ariboflavinosis and 1 had polyneuritis due to lack of thiamine. The hospitalized patients without clinical evidence of deficiency disease were all members of the lower income group of the population, and their dietary histories often indicated an inadequate supply of the vitamin B complex. The diseases for which these persons entered the hospital were such that in many instances there may have been poor absorption or increased need of vitamins. The amount of nicotinic acid and its derivatives excreted was determined for each subject in one or more of the following circumstances: (1) in twenty-four hours with no administration of nicotinic acid or its derivatives; (2) in twenty-four hours after oral or parenteral administration of 100 mg. of nicotinic acid, sodium nicotinate or nicotinamide; (3) in twenty-four hours after oral administration of 300 mg. of nicotinamide, and (4) in six hours after oral administration of 300 mg. of nicotinamide. Prior to each of these examinations, the patient was given a diet from which foods with high content of trigonelline (coffee, nuts and leguminous vegetables) were omitted. Such a diet is essential to the test, since nicotinic acid is excreted in the urine largely as trigonelline.

METHOD

The method used for the determination of nicotinic acid and its derivatives was that of Perlzweig, Levy and Sarett [2a] with minor modifications, including several suggested by Dann and Handler.[5] Five to 20 cc. of urine, the amount depending on the probable concentration of nicotinic acid, was concentrated, hydrolyzed, adjusted to p_H 0.5 to 1, adsorbed on and eluted from Lloyd's reagent and treated with lead nitrate, as outlined by Perlzweig. The lead was removed by adding normal potassium phosphate (K_3PO_4) until a permanent faint pink color was obtained with phenolphthalein as an indicator. After centrifugation, the supernatant fluid was poured off and the acidity adjusted to p_H 4.5, alkaline-acid test paper being used as an indicator.

Technical assistance was rendered by Herschel Welch, M.S., Lillian Kyame, B.S., and Shirley Cordill, B.A.

From the Department of Medicine, School of Medicine, Tulane University and Charity Hospital of Louisiana.

Aided in part by a grant from the Eli Lilly Company to the Department of Tropical Medicine, Tulane University School of Medicine.

1. (*a*) Field, H., Jr.; Melnick, D.; Robinson, W. D., and Wilkinson, C. F., Jr.: Studies on the Chemical Diagnosis of Pellagra (Nicotinic Acid Deficiency), J. Clin. Investigation **20**:379, 1941. (*b*) Melnick, D., and Field, H., Jr.: Determinations of Nicotinic Acid by Means of Photoelectric Colorimetry, J. Biol. Chem. **134**:1, 1940.

2. (*a*) Perlzweig, W. A.; Levy, E. D., and Sarett, H. P: Nicotinic Acid Derivatives in Human Urine and Their Determination, J. Biol. Chem. **136**:729, 1940. (*b*) Sarett, H. P.; Huff, J. W., and Perlzweig, W. A.: Studies in Nicotinic Acid Metabolism: I. The Fate of Nicotinic Acid in Man, J. Nutrition **23**:23, 1942.

3. Perlzweig, W. A.; Sarett, H. P., and Margolis, L. H.: Studies in Nicotinic Acid Metabolism: V. A Test for Nicotinic Acid Deficiency in Man, J. A. M. A. **118**:28 (Jan. 3) 1942.

4. Goldsmith, G. A.: Evaluation of Nicotinic Acid Nutrition by Studies of Urinary Excretion, Proc. Soc. Exper. Biol. & Med. **51**:42, 1942.

5. Dann, W. J., and Handler, P.: The Quantitative Estimation of Nicotinic Acid in Animal Tissues, J. Biol. Chem. **140**:201, 1941.

The development of color with cyanogen bromide and paramethylaminophenol sulfate was carried out as indicated by Perlzweig [2a] except that 1 cc. of 10 per cent potassium biphosphate (KH_2PO_4) was added to each of the tubes. After one hour during which the tubes were kept in the dark to permit the development of color, readings were made in a Klett-Summerson photoelectric colorimeter, using a no. 511 Corning filter. In each experiment a standard solution of nicotinic acid (containing 10 or 20 micrograms) was subjected to development of color. A reagent blank was prepared, as was a blank for the correction for residual color in the test solution obtained from urine.

In the determination of trigonelline the method of Perlzweig was followed, except that double the quantity of urea and alkali was used in most of the experiments. Larger amounts of trigonelline were recovered with this procedure, although the recoveries fell considerably short of those reported by Perlzweig.

The method for the determination of acid-hydrolyzable derivatives of nicotinic acid [6] was highly satisfactory. The average recovery of nicotinic acid added to urine in a series of 38 tests was 98.03 ± 1.98 per cent. Nicotinamide was recovered equally well. The method for the determination of trigonelline, however, permitted recovery of only 40 to 50 per cent of the amount added. Nevertheless, repeated analyses of the same urine on different days and with samples of various sizes gave consistent results in most instances. The figures for trigonelline throughout this paper are given as nicotinic acid and represent the amount actually determined by analysis.

Urine was preserved with toluene, and if not tested immediately after collection it was autoclaved at 15 pounds' (6.8 Kg.) pressure for fifteen minutes, after the reaction had been adjusted to p_H 7. In 13 experiments there was no loss when tests were repeated after two to thirteen days. Neither toluene nor sulfuric acid was a satisfactory preservative when urine was stored longer than twenty-four hours.

OBSERVATIONS

Excretion of Nicotinic Acid and its Derivatives in the Urine in Twenty-Four Hours.—Studies were made on 10 normal persons and 37 hospitalized patients, of whom 12 had clinical evidence of nicotinic acid deficiency and 2 of ariboflavinosis. The nicotinic acid deficiency was complicated by peripheral neuritis in 1 patient and by a lack of riboflavin in 4 others. The results are given in the table. There was no difference in the amount of nicotinic acid (acid-hydrolyzable derivatives) excreted by normal persons and by patients with or without deficiency disease. The amount of trigonelline excreted, however, was lowest in patients with pellagra and ariboflavinosis, highest in normal persons and intermediate in the hospitalized patients without obvious vitamin deficiency. The level of excretion of the 2 patients with evidence of only ariboflavinosis was as low as that of patients with lesions of both nicotinic acid and riboflavin deficiency. Since there is considerable overlapping of the findings for the three groups, estimation of the excretion of either trigonelline or total derivatives of nicotinic acid in a twenty-four hour specimen of urine is an unsatisfactory test of the adequacy of nutrition in relation to nicotinic acid in a given patient.

The figures listed in the table are corroborative of those of several other investigators. Perlzwig and his co-workers [2b] reported an average excretion of 1.2 mg. of nicotinic acid and 15.1 mg. of trigonelline in twenty-four hour specimens of urine for 33 normal subjects. In 12 hour specimens [3] the average output of trigonelline was 10 mg. for normal persons and 7.7 mg. for hospitalized patients. Field,[1a] using a different chemical method, found an average daily excretion of 3.8 mg. of nicotinic acid and 19.5 mg. of trigonelline for 10 normal persons, while for 7 subjects with vitamin deficiency the excretion of nicotinic acid averaged 2.7 mg. and that of trigonelline 3.1 mg.

Excretion of Derivatives of Nicotinic Acid in the Urine in Twenty-Four Hours

		Nicotinic Acid,* Mg.			Trigonelline, Mg.			Total, Mg.		
Subjects	Number of Subjects	Minimum	Maximum	Average	Minimum	Maximum	Average	Minimum	Maximum	Average
Normal.....	10	0.9	1.6	1.2	8.5	21.1	14.4	9.5	22.1	15.6
Hospitalized †...	23	0.5	3.0	1.4	2.5	25.2	9.6	3.5	26.6	11.0
Vitamin deficient	14	0.1	1.6	1.0	1.1	21.4	8.4	1.2	22.8	9.4

* Acid-hydrolyzable derivatives of nicotinic acid.
† Hospitalized patients with no clinical evidence of deficiency disease.

Excretion of Nicotinic Acid and its Derivatives in the Urine in Twenty-Four Hours Following the Administration of 100 mg. of Nicotinic Acid, Sodium Nicotinate or Nicotinamide.[7]—Nineteen persons for whom the urinary excretion of nicotinic acid in twenty-four hours had been measured were given test doses of 100 mg. of nicotinamide parenterally (10 persons), sodium nicotinate parenterally (6 persons) or nicotinic acid orally (3 persons). Chart 1 shows the total excretion of derivatives of nicotinic acid (both nicotinic acid and trigonelline) in twenty-four hours after the administration of the test dose and also indicates the amount of the 100 mg. dose which was recovered in this period obtained by subtracting from the total amount excreted the quantity present in the control twenty-four hour specimen. Normal persons excreted larger amounts of nicotinic acid derivatives after the test dose than did either group of hospitalized patients. Greater differences are observed if

6. In the remainder of this paper, acid-hydrolyzable derivatives of nicotinic acid will be referred to as nicotinic acid.

7. The nicotinic acid, sodium nicotinate and nicotinamide were supplied by Merck and Company.

the total amount excreted in twenty-four hours after the test dose is considered rather than the extra amounts excreted. That is, the test dose magnifies the differences previously noted in the control measurement of the twenty-four hour excretion. This test, however, will not completely differentiate normal from deficient

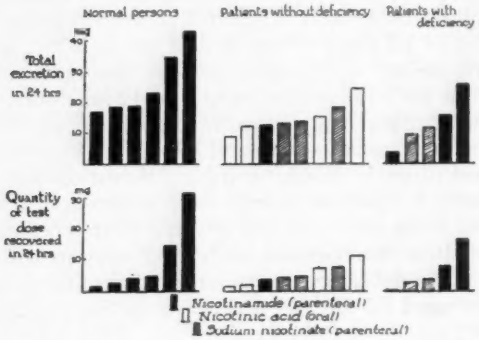

Chart 1.—Urinary excretion of derivatives of nicotinic acid in twenty-four hours after a test dose of 100 mg. of nicotinamide, sodium nicotinate or nicotinic acid.

subjects. The output in 1 deficient patient (with ariboflavinosis) exceeded that of several normal persons. The 4 patients with pellagra excreted less than did the normal subjects, as did 6 of the 8 hospitalized patients without clinical signs of vitamin deficiency. The results were similar for each of the test substances administered, except that nicotinamide was excreted almost entirely as trigonelline, while sodium nicotinate and nicotinic acid increased the excretion of both trigonelline and acid-hydrolyzable derivatives of nicotinic acid.

Excretion of Nicotinic Acid and its Derivatives in Twenty-Four Hours after the Oral Administration of 300 mg. of Nicotinamide.—This test was performed on 31 persons, 10 normal subjects, 13 hospitalized patients without clinical evidence of deficiency disease and 8 patients with deficiency of the vitamin B complex (7 with nicotinic acid deficiency and 1 with ariboflavinosis). Chart 2 shows the total output of derivatives of nicotinic acid in twenty-four hours after 300 mg. of nicotinamide was given orally. The quantity of the test dose which was recovered in this period is also indicated. The additional excretion was calculated by subtracting the amount excreted in the control period of twenty-four hours. Nine of the 10 normal persons excreted more than 40 mg. of derivatives of nicotinic acid in the urine after the test dose. In only 1 patient with deficiency disease was the output above 40 mg. This subject had glossitis characteristic of an inadequate supply of nicotinic acid. About one half of the hospitalized patients without clinical evidence of vitamin deficiency excreted more and the other half less than 40 mg. The figures which indicate the extra excretion, that is, the increment after the test dose, show a similar distribution. From normal persons, with 1 exception, 25 mg. or more of the test dose was recovered; from deficient subjects, with the 1 exception already discussed less than 25 mg. was recovered, while for hospital patients without vitamin deficiency the recovery in approximately half the instances was less and in half more than 25 mg. It appears to be unnecessary to measure the excretion in a control period. Measurement of the total excretion in twenty-four hours after the test dose gives information similar to that obtained from estimation of the quantity of test material recovered.

The findings reported here may be compared with those of Perlzweig, Sarett and Margolis,[3] who determined the extra excretion of total nicotinic acid in twelve hours after giving 500 mg. of nicotinamide. They found that normal persons excreted a larger quantity of the test dose than did undernourished subjects from a National Youth Administration camp, while a group of hospitalized patients excreted a still smaller amount. The studies of Perlzweig and his associates and those reported here suggest that the amount of the derivatives of nicotinic acid excreted after ingestion of a test dose of nicotinamide gives some indication of the state of nutrition in relation to nicotinic acid.

Urinary Excretion of Nicotinic Acid and its Derivatives in Six Hours after the Oral Administration of 300 mg. of Nicotinamide.—In view of

Normal persons
Hospital patients without deficiency
Patients with deficiency
Total excretion in 24 hrs
Quantity of test dose recovered in 24 hrs

Chart 2.—Urinary excretion of derivatives of nicotinic acid in twenty-four hours after the oral administration of 300 mg. of nicotinamide.

the difficulties involved in collecting twenty-four hour specimens of urine, the excretion in six hours was determined in 29 of the 31 subjects who received 300 mg. of nicotinamide. It was found that the output of nicotinic acid and its derivatives in six hours measured approximately 50 per cent of the excretion in twenty-four hours

(chart 3). The shorter test gives information comparable to that derived from the longer one.

Accordingly, the quantity of derivatives of nicotinic acid excreted in the urine in six hours after the administration of 300 mg. of nicotinamide was determined for 44 subjects, 13 normal persons, 13 hospitalized patients without vitamin

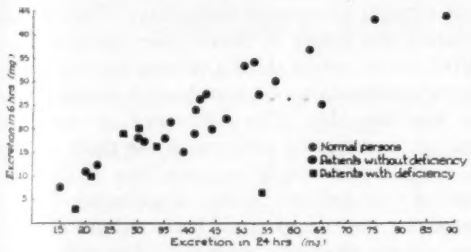

Chart 3.—Comparison of urinary excretion of derivatives of nicotinic acid in six hours with that in twenty-four hours after the oral administration of 300 mg. of nicotinamide.

deficiencies and 18 patients with deficiency of the vitamin B complex. Eight of the deficient subjects had typical pellagra, 8 had nicotinic acid deficiency without dermatitis, 1 had thiamine deficiency and 1 had riboflavin deficiency. The nicotinic acid deficiency was complicated in 5 instances by ariboflavinosis and in 2 by peripheral neuritis due to lack of thiamine hydrochloride.

In performing the six hour excretion test it is essential to administer enough fluid to obtain a volume of urine of at least 200 cc. There is no quantitative relationship between the total excretion of nicotinic acid and the volume of urine, but when the output of fluid is extremely small the subject's maximum excretion of nicotinic acid may not be obtained. The results for the 44 persons who were given the six hour test are presented in chart 4. The minimum excretion for normal subjects after an oral test dose of 300 mg. appears to be between 20 and 25 mg. in six hours. Of 13 normal persons, only 2 excreted less than 23 mg. Repetition of the test on several occasions for 3 of the subjects gave results which checked within a few milligrams. Five of the hospitalized patients without evidence of deficiency disease excreted 20 mg. or more in six hours; 8 excreted less than this amount. Fifteen of the 18 patients with clinical signs of deficiency of nicotinic acid and/or the other B vitamins excreted 20 mg. or less in the test period. The amount excreted did not vary directly with the severity of the pellagra. A number of the hospitalized patients with acute and chronic disease excreted as small a quantity of nicotinic acid and its derivatives as did some patients with pellagra. In all likelihood these findings indicate a subclinical nicotinic acid deficiency. The previous diet of these patients had been poor, and the intake, absorption and utilization of nutrients were complicated by organic disease. In other deficiency states, such as those due to an inadequate supply of thiamine or of ascorbic acid, laboratory tests often show diminished excretion of the respective vitamin prior to the appearance of clinical signs of deficiency. Similar findings might be anticipated in nicotinic acid deficiency.

The 3 subjects with clinical evidence of vitamin deficiency who had levels of excretion in the range of the normal subjects (above 20 mg.) warrant comment. One had acute hepatitis following arsenical therapy for syphilis, the second had cirrhosis of the liver and the third had chronic alcoholism and polyneuritis. The first 2 patients had both glossitis and cheilosis, indicative of riboflavin and nicotinic acid deficiency, and, in addition, definite signs of severe hepatic disease. The third patient had evidence only of thiamine deficiency, and the bodily stores of nicotinic acid may have been adequate. Impairment of hepatic function may have been present in this patient also, in view of the history of chronic alcoholism, but special tests were not performed. The findings suggest the possibility that when hepatic function is abnormal the body may be unable to retain and utilize nicotinamide. However, many factors doubtless influence the excretion of nicotinic acid, and nicotinic acid is probably excreted in forms other than those which were measured with the chemical methods used.[8]

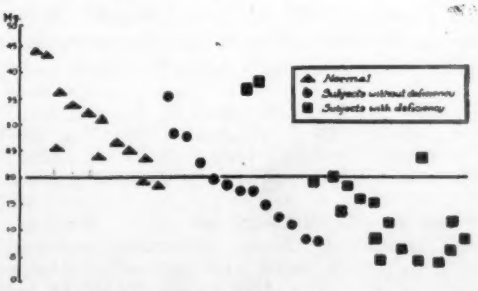

Chart 4.—Urinary excretion of derivatives of nicotinic acid in six hours after the oral administration of 300 mg. of nicotinamide.

Two patients with pellagra[9] were given the six hour test of excretion of nicotinic acid at

8. Najjar, V. A.; Stein, H. J.; Holt, L. E., Jr., and Kobler, C. V.: Excretion of Specific Fluorescent Substances in Urine in Experimental Nicotinic Acid Deficiency, J. Clin. Investigation **21**:236, 1942.

9. The findings for these patients are not included in chart 4.

the time of entrance to the hospital and after a period of therapy with nicotinic acid. One patient, a Negro woman aged 26, excreted 9.8 mg. of derivatives of nicotinic acid when tested before any therapy was given. She received 300 mg. of nicotinamide daily for four weeks. When retested at the end of this period, she excreted 16.3 mg. All evidence of pellagra had disappeared, except for pigmentation of the skin on the backs of the hands, and that was decreasing in intensity. The other patient, a white girl 10 years of age, excreted 8.8 mg. of derivatives of nicotinic acid when the test dose was given shortly after admission to the hospital. She received 200 mg. of nicotinic acid daily for three weeks, and repetition of the test showed an excretion of 11.9 mg. This patient was greatly improved at the time of the second test but still showed slight pigmentary changes. No nicotinic acid was given to either of these subjects for two days before the second test was performed. These data lend support to the validity of the six hour excretion test as a measure of the status of nutrition with regard to nicotinic acid.

SUMMARY

The urinary excretion of nicotinic acid and its derivatives was studied for 63 persons under various experimental conditions. The total excretion of derivatives of nicotinic acid was greatest in normal persons, next highest in hospitalized patients without evidence of deficiency disease and lowest in patients with pellagra and vitamin B complex deficiency. This is true whether the output in twenty-four hours is measured or the output during various intervals after the administration of a test dose of nicotinic acid or nicotinamide. The difference in the total amount excreted by subjects in the three groups is due almost entirely to variations in the output of trigonelline. The administration of a large test dose of nicotinic acid, sodium nicotinate or nicotinamide magnifies this difference. Measurement of the quantity of derivatives of nicotinic acid excreted in six hours following the oral administration of 300 mg. of nicotinamide is suggested as a useful procedure in evaluating the nutritional status of a person with regard to nicotinic acid.

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SUBACUTE ENDOCARDITIS ASSOCIATED WITH INFECTION WITH A SPIRILLUM

REPORT OF A CASE, WITH REPEATED ISOLATION OF THE ORGANISM FROM THE BLOOD

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Clinical syndromes following rat bite have been ascribed to two micro-organisms, Streptobacillus moniliformis (Streptothrix, as originally described by Schottmüller) and Spirillum minus. The latter organism is of special interest in connection with the case about to be reported.

The present concept that rat bite fever is due to infection with a spirillum dates back to 1916, when Futaki, Takaki, Taniguchi and Osumi [1] described an unnamed spirochetal micro-organism as "the cause of rat-bite fever." One year later Futaki and his associates [2] termed this organism Spirochaeta morsus muris. On the basis of morphologic characteristics, especially the rigid body and the terminal flagellums, Robertson [3] preferred to classify the causal agent of rat bite fever (sodoku) as a spirillum. In view of the resemblance of the terminal flagellums to the minus sign, he proposed to adopt the name Spirillum minus, originally given by Carter,[4] for an organism isolated from a rodent.

The etiologic relation of S. minus to rat bite fever has been established beyond doubt, although the literature reveals that, at least in the United States, a disease with a clinical picture indistinguishable from that of rat bite fever is caused more frequently by Str. moniliformis than by the spirillum. Brown and Nunemaker [5] implied that some patients with rat bite fever may have been infected with both organisms.

Cases of rat bite fever due to S. minus have occurred only endemically in the United States. One set of studies has been concerned with cases in which the diagnosis was made on the basis of a typical clinical picture and a definite history of rat bite. Among these cases were many in which the diagnosis was made by inoculation of laboratory animals (mice, rats and guinea pigs) with material from the lymph nodes [6] or the patient's blood [7] and subsequent dark field observation of the micro-organism in the blood of the inoculated animals. In several of these cases S. minus was observed on direct dark field examination of the patient's blood [8] and of material from the wound,[6b] and in some cases bacteriologic confirmation was not obtained.[9]

To another group of cases belong those in which the occurrence of an animal bite was either denied or not recognized.[10] Animal inoculations, however, proved that S. minus was the causative organism.

A review of the subject of rat bite fever leaves one with the impression that, despite positive reports, the isolation of S. minus from the patient's blood has thus far not been clearly successful. Bayne-Jones,[11] in 1931, quoted a personal communication from the Japanese investigators Futaki, Takaki, Taniguchi and Osumi [1]

From the Laboratories and the Second Medical Service of Dr. Eli Moschcowitz, the Mount Sinai Hospital.

1. Futaki, K.; Takaki, I.; Taniguchi, T., and Osumi, S.: The Cause of Rat-Bite Fever, J. Exper. Med. **23**:249-250, 1916.

2. Futaki, K.; Takaki, I.; Taniguchi, T., and Osumi, S.: Spirochaeta Morsus Muris, N. Sp., the Cause of Rat-Bite Fever, J. Exper. Med. **25**:33-44, 1917.

3. Robertson, A.: Observation on the Causal Organism of Rat-Bite Fever in Man, Ann. Trop. Med. **18**:157-175, 1924.

4. Carter, H. V.: Note on the Occurrence of a Minute Blood Spirillum in an Indian Rat, Scient. Mem. Med. Off. India, 1887, pt. 3, p. 45.

5. Brown, T., and Nunemaker, J. C.: Rat-Bite Fever: A Review of the American Cases with Re-evaluation of Etiology; Report of Cases, Bull. Johns Hopkins Hosp. **70**:202-327, 1942.

6. Gilkey, H. M., and Dennie, C. C.: Rat-Bite Fever in Children, South. M. J. **32**:1109-1111, 1939. Woolley, P. V., Jr.: Rat-Bite Fever: Report of a Case with Serologic Observations, J. Pediat. **2**:693-696, 1936.

7. Lamb, A. R., and Paton, F. W.: A Case of Vegetative Endocarditis Caused by Hitherto Undescribed Spirillum (Spirillum Surati, N. S.), Arch. Int. Med. **12**:259-272 (Sept.) 1913.

8. Low, C. G.: A Case of Rat-Bite Fever in England, Brit. M. J. **1**:236, 1924. Lamb and Paton.[7] Rogliano, A. G.: Two Cases of Rat-Bite Fever, Surgery **11**:632-635, 1942.

9. Arkin, A.: Rat-Bite Fever: A Case Report, West Virginia M. J. **15**:281-284, 1920-1921. Gilkey and Dennie.[6]

10. Walker, H.: Rat-Bite Fever: Report of Two Cases, Virginia M. Monthly **64**:272-275, 1937. Lamb and Paton.[7]

11. Bayne-Jones, S.: Rat-Bite Fever in the United States, Internat. Clin. **3**:235-253, 1931.

in which they withdrew their previous claim of having been able to grow the spirillum on Shimamine's medium. Attempts by Robertson,[8] Knowles and Das Gupta [12] and McDermott [13] to repeat Jodes's [14] cultivation of the micro-organism on a modified form of Vervoort's medium were never successful.

Foncannon [15] reported the cultivation of "Spirochaeta morsus muris" from the patient's blood in 1 case. He failed, however, to mention the method employed. In 1930 Douthwaite [16] reported that actively motile spirilla were observed from trypsinized bullock's heart inoculated with patient's blood. Mice were inoculated with the culture, and the micro-organism persisted in the peripheral circulation for a few days. In 1913 Lamb and Paton [7] isolated a spirillum from the blood of a patient with subacute endocarditis. They named the organism Spirillum surati, after the locality in India in which the disease was presumably contracted. It will be seen later that the ease with which the micro-organism grew after a short period of incubation makes its nature somewhat doubtful.

Recently, in Mount Sinai Hospital, we have had under study an unusual case of subacute endocarditis in which the causative micro-organism was S. minus. The causal relation of this organism to the endocarditis was suggested by clinical and serologic observations and was established bacteriologically. Pathologic and bacteriologic confirmation was obtained at autopsy. The relation of this micro-organism to the causative spirillum of rat bite fever was suggested by its morphologic characteristics, the serologic evidence and the behavior in mice.

REPORT OF CASE

A man aged 23 entered Mount Sinai Hospital (service of Dr. Eli Moschcowitz) on March 28, 1942.

Past History.—The patient had worked on a tanker between Texas and New York and as a truck helper about freight yards. There was no history suggestive of syphilis, rheumatic fever or chorea. A Wassermann test of the blood made elsewhere was reported to give a negative reaction.

Previous Illness.—About two months before his admission to the hospital the patient had fever, with a temperature of 105 F., and a pain in the right side of the chest. A physician made the diagnosis of pneumonia with pleurisy, and sulfonamide compounds were administered. The patient recovered.

Five weeks before admission to Mount Sinai Hospital he had a dizzy spell, followed by a chill, and his temperature rose to 103 F. He complained of headache, recurring spells of dizziness, stiffness of the neck and tenderness and pain in the left upper abdominal quadrant. These symptoms persisted for three days, and he was admitted to a hospital with the probable diagnosis of meningitis.

Clinical Course: On admission (in February 1942) the temperature was 100.8 F. and the pulse rate 95 a minute. The patient appeared acutely ill. The lungs were clear. The heart beat was regular; there were a loud, blowing systolic murmur at the apex, and a high-pitched diastolic murmur to the left of the sternum in the third intercostal space. The abdomen was moderately tender, with "splinting" in the left upper quadrant. The spleen was felt 1 fingerbreadth below the costal margin. The liver was palpable. Neurologic examination revealed no abnormality except for stiffness of the neck.

Laboratory Data: The red blood corpuscles numbered 4,000,000; the hemoglobin measured 10.5 Gm. per hundred cubic centimeters, and the white cell count was 8,000, with 55 per cent polymorphonuclear leukocytes and 34 per cent lymphocytes. The urine contained no protein or dextrose; agglutination tests of the blood serum gave negative reactions for typhoid and brucellosis; the test for heterophil antibodies gave a negative reaction. The Wassermann reaction of the blood was 4 plus; the Hinton reaction was positive, and the Kline reaction was 2 plus. Two spinal punctures were made. The first spinal tap induced trauma; the pressure was 160 mm. of water; the reaction for globulin was 3 plus; the Wassermann reaction was 4 plus, and culture of the fluid yielded no growth. The second spinal tap yielded clear fluid; the pressure was not increased; the reaction for globulin was negative; the Wassermann reaction was 3 plus, and the colloidal gold curve was characteristic of dementia paralytica. There were no cells.

The patient's temperature dropped, and the headache and stiffness of the neck disappeared within three or four days after his admission. He was discharged on March 6 to the antisyphilitic clinic for treatment. It may be added that the serologic reactions of both parents were negative.

Physical Status Prior to Admission to Mount Sinai Hospital.—The patient had already received several injections of a bismuth preparation before he consulted one of us (W. M. H.), on March 24. He complained of remittent malaise, chilliness and excessive perspiration. There was severe pain in the left thumb, and a small, nontender ecchymotic area was present over each ankle. An aortic diastolic murmur and an apical systolic murmur, radiating to the left axilla, were audible. Sediment from a centrifuged specimen of the urine contained a few red blood cells per high power field.

In view of the unusual prodromal course, the absence of a positive history of syphilis, the presence of the audible murmurs of aortic and mitral insufficiency, the firm spleen, which was palpable 2 fingerbreadths below the costal margin, the embolic lesions, the presence of occasional red blood cells in the urine and the relative well-being of the patient, the diagnosis of subacute bacterial endocarditis superimposed on rheumatic heart disease was made.

The positive Wasserman reaction was thought to be a pseudoreaction to the existing infection. With this

12. Knowles, R., and Das Gupta, B. M.: Rat-Bite Fever as an Indian Disease, Indian M. Gaz. **63**:493-512, 1928.

13. McDermott, E. N.: Rat-Bite Fever: A Study of the Experimental Disease, with a Critical Review of the Literature, Quart. J. Med. **21**:433-458, 1928.

14. Jodes, T.: Cultivation of the Spirillum of Rat-Bite Fever, Lancet **2**:1225-1226, 1925.

15. Foncannon, F.: Rat-Bite Fever, J. Kansas M. Soc. **31**:331-333, 1930.

16. Douthwaite, A. H.: Rat-Bite Fever, Guy's Hosp. Gaz. **44**:438-441, 1930.

diagnosis he was referred to the Mount Sinai Hospital for further study.

Clinical Course at Mount Sinai Hospital.—On the patient's admission to the hospital, the physical findings of the referring physician, described previously, were confirmed. The lesions of the ankle and thumb were no longer visible or palpable, and no other embolic lesions were present.

The provisional diagnoses were subacute bacterial endocarditis, possibly superimposed on rheumatic cardiovalvular disease, and syphilitic aortitis, with aortic insufficiency to be ruled out.

The following clinical notes were taken during the patient's stay in the hospital: . . .

March 30: The hemoglobin concentration was 87 per cent; the white blood cell count was 7,750, with 46 per cent segmented and 10 per cent nonsegmented polymorphonuclear leukocytes, 34 per cent lymphocytes, 7 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The Wassermann reaction of the blood was 4 plus and the Kahn reaction 3 plus. The specific gravity of the urine was 1.030; the urine contained no protein or sugar and only an occasional red blood cell. Culture of a specimen of blood taken at this time was reported to yield no growth four days later.

April 1: The sedimentation rate of erythrocytes by the Cutler tube method was 18 mm. in one hour and six minutes, a normal value.

April 3: A roentgenogram of the chest revealed no abnormality of the heart or lungs. A specimen of the blood taken at this time and cultured in an atmosphere of 3.5 per cent carbon dioxide was reported six days later to be positive for a micro-organism resembling S. minus, the causative organism of rate bite fever.

April 7: The cerebrospinal fluid was clear and the pressure normal. The Pandy reaction was 4 plus; the reaction for globulin was plus-minus; the sugar content was 55 mg. per hundred cubic centimeters; Wassermann reaction was negative, and the colloidal gold curve was 1111100000.

April 9: The Wassermann reaction of the blood was 4 plus, and the Kahn reaction, 3 plus. The tuberculin patch test gave a negative reaction. The Frei test was negative for lymphogranuloma venereum. A blood culture was reported positive six day later for a micro-organism resembling S. minus.

April 15: The diagnosis of subacute endocarditis due to infection with a spirillum was now suggested as an explanation for both the clinical course and the serologic reactions.

April 20: The patient complained of pain in the tip of the fourth finger of the left hand. The area was tender to pressure, but there were no external manifestations of embolism.

April 21: The optic disks were normal. An intravenous injection of 0.5 Gm. of tryparsamide was given. A fourth blood culture was reported positive for S. minus six days later.

April 27: Prior to this date the patient displayed almost normal strength and was apparently free from symptoms; he often asked to be discharged. A painful area suddenly developed on the anterolateral aspect of the left ankle. There was no redness or edema at the site of maximum tenderness. A diagnosis of tenosynovitis of the tendons of the extensor muscles was made.

April 28: Neoarsphenamine, 0.1 Gm., was injected intravenously.

April 30: Neoarsphenamine, 0.2 Gm., was given intravenously.

May 2: Neoarsphenamine, 0.13 Gm., was given intravenously. The blood culture was reported negative for the spirillum twelve days later.

May 4: The hemoglobin was 82 per cent, and the white blood cell count, 6,300, with 45 per cent segmented and 14 per cent nonsegmented polymorphonuclear leukocytes, 34 per cent lymphocytes, 6 per cent monocytes and 1 per cent plasma cells.

May 5: Except for unusual axis deviation, the electrocardiogram was normal.

May 8: Neoarsphenamine, 0.4 Gm., was given intravenously.

May 9: The sixth blood culture was reported positive for S. minus five days later.

May 13: The Wassermann reaction of the blood was 4 plus, and the Kahn reaction 3 plus. Neoarsphenamine, 0.5 Gm., was given intravenously. The temperature rose to 102 F. It was observed that similar elevations, to between 101 and 102.8 F., had occurred previously at approximately thirteen to seventeen day intervals.

May 20: In view of the apparent ineffectiveness of neoarsphenamine, the five day continuous drip method of arsenical medication was begun, under the direction of Dr. L. Chargin. Half the therapeutic dose usually given to syphilitic patients, i. e., 0.12 Gm. of mapharsen in 500 cc. of 5 per cent dextrose, was administered, without febrile or other untoward reactions.

May 21: Mapharsen, 0.12 Gm. in 500 cc. of 5 per cent dextrose, was given intravenously. The hemoglobin concentration was 85 per cent; the white blood cells numbered 7,500, with 33 per cent segmented and 8 per cent nonsegmented polymorphonuclear leukocytes, 46 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils and 2 per cent basophils. The spleen was not tender and was enlarged to 2 or 3 fingerbreadths below the costal margin.

May 22: Mapharsen, 0.12 Gm. in 500 cc. of 5 per cent dextrose, was given intravenously. The hemoglobin concentration was 80 per cent, and the white blood cells numbered 4,500, with a differential count similar to that on the preceding day.

May 23: Mapharsen, 0.12 Gm. in 500 cc. of dextrose, was given intravenously. The hemoglobin concentration was 79 per cent, and the white blood cells numbered 6,200.

May 24: Mapharsen, 0.12 Gm., in 500 cc. of dextrose, was given intravenously.

May 25: A blood culture was reported to be negative for the spirillum ten days later.

May 26: Despite the administration of 0.6 Gm. of mapharsen within five days, the serologic reactions remained unchanged.

May 28-30: In the midst of the patient's apparent "good health," pain suddenly developed in the left upper abdominal quadrant and the left shoulder. This was attributed to a splenic infarct, probably at the upper pole. It served to indicate that an active valvular process was still smoldering, despite the negative report on the last blood culture. The spleen was not tender, nor had it increased significantly in size. Although the urine had almost continuously shown varying traces of protein and microscopic evidence of blood, the incident of pain was the first clearcut evidence of visceral embolization observed in the hospital.

June 2: The blood culture was reported positive for S. minus six days later.

June 9: The blood culture was reported positive for S. minus six days later.

June 12: Two small circular erythematous macules, about 5 mm. in diameter, were noted on the outer aspect of the sole of the left foot.

June 13: Because the usual antisyphilitic arsenicals were ineffective in altering the clinical course and the positive blood culture, 1 Gm. of tryparsamide was administered intravenously, at the suggestion of Dr. Chargin.

June 15: Three small round, tender macules appeared on the sole of the left foot. Again, severe pain in the left upper abdominal quadrant radiated to the left shoulder and was intensified by deep breathing. The spleen was now tender.

June 16: A tender, erythematous lesion appeared under the nail of the third right finger. The highest temperature for the past seventeen days was 100.6 F. An abnormal sedimentation rate of twenty minutes was reported. The Wassermann reaction of the blood was 4 plus, and the Kahn reaction was 1 plus.

June 18: The temperature rose to 103.8 F. Two tender, violaceous, slightly raised lesions, of 0.5 inch (1.27 cm.) diameter, appeared on the hypothenar eminence of each hand. The tenth blood culture was reported negative for S. minus eighteen days later.

June 19: The white blood cell count was 7,250.

June 20: Tryparsamide, 2 Gm., was given intravenously.

June 21: A fresh petechia was noted over the right external malleolus. There suddenly developed pain in the occiput, nausea, projectile vomiting, painful flexion of the neck and a rise in blood pressure to 220 systolic and 70 diastolic. It was the clinical impression that the patient had sustained a subarachnoid hemorrhage.

June 22: Pulmonary edema developed, and the patient died.

Bacteriologic Data.—Cultivation of S. minus from the Blood: Ten specimens of blood were taken for culture. They were obtained at the bedside in the following routine manner:[17] Twenty-three cubic centimeters of the patient's blood was drawn from an anterior cubital vein. Fifteen cubic centimeters was divided equally among three 100 cc. Erlenmeyer flasks, the first containing veal infusion broth, p_H 7.4; the second, 2 per cent dextrose–veal infusion broth, p_H 7.4; and the third, 10 per cent tomato extract–veal infusion broth, p_H 7.6.[18] The remaining 8 cc. of blood was equally divided to form three pour plates: Two cubic centimeters was mixed with each of two tubes containing 12 cc. of 2 per cent dextrose–veal infusion agar, p_H 7.4; 2 cc. was mixed with a tube containing 12 cc. of plain veal infusion agar, p_H 7.4, and 2 cc. was put into a tube containing 10 cc. of cooked liver broth, p_H 7.4, which was sealed with 2 cc. of sterile petrolatum. Gram stains of samples from the flasks were made each day.

As is shown in table 1, the first specimen of blood, which was incubated under aerobic and anaerobic con-

TABLE 1.—*Bacteriologic Data on Blood Cultures in a Case of Rat Bite Fever*

Blood Culture						
Date	No.	Mediums Used *	Mediums in Which Micro-Organism Grew *	Length of Incubation, Days	Specimen Taken, Day After Treatment	Treatment Employed
3/30	1	Routine	No growth	4, under aerobic and anaerobic conditions	.....	None
4/ 3	2	Routine	1 2% dextrose flask; 1 tomato flask	6, in approximately 3.5% carbon dioxide and under anaerobic conditions	.....	None
4/ 9	3	Routine	1 2% dextrose flask; 1 tomato flask	6, in approximately 3.5% carbon dioxide and under anaerobic conditions	.....	None
4/21	4	Routine	1 2% dextrose flask; 1 tomato flask	6, in approximately 3.5% carbon dioxide and under anaerobic conditions	.....	None
5/ 2	5	1 plain flask; 2 2% dextrose flasks; 2 tomato flasks	No growth	12 in approximately 3.5% carbon dioxide	Third	4/21 Tryparsamide, 0.5 Gm., intravenously 4/28 Neoarsphenamine, 0.1 Gm., intravenously 4/30 Neoarsphenamine, 0.2 Gm., intravenously
5/ 9	6	3 2% dextrose flasks; 2 tomato flasks	1 2% dextrose flask; 1 tomato flask	5, in approximately 3.5% carbon dioxide	First	5/2 Neoarsphenamine, 0.3 Gm., intravenously 5/8 Neoarsphenamine, 0.4 Gm., intravenously
5/25	7	2 2% dextrose flasks; 3 tomato flasks	No growth	11, in approximately 3.5% carbon dioxide	First	5/13 Neoarsphenamine, 0.5 Gm., intravenously 5/20 Mapharsen, 0.13 Gm. in 500 cc. of 5% dextrose 5/21, 5/22, 5/23 and 5/24 Mapharsen, 0.13 Gm. in 500 cc. of 5% dextrose
6/ 2	8	2 2% dextrose flasks; 3 tomato flasks	1 tomato flask	9, in approximately 3.5% carbon dioxide	.....	None
6/ 9	9	2 2% dextrose flasks; 3 tomato flasks	3 tomato flasks	6, in approximately 3.5% carbon dioxide	.....	6/13 Tryparsamide, 1.0 Gm., intravenously
6/18	10	2 2% dextrose flasks; 3 tomato flasks	No growth	18, in approximately 3.5% carbon dioxide	Fifth	6/20 Tryparsamide, 2 Gm., intravenously

* The mediums containing 2 per cent dextrose and 10 per cent tomato extract were made up with veal infusion broth.

17. Shwartzman, G., and Goldman, J. L.: Streptococcus Haemolyticus Bacteremia, Arch. Surg. **34**:82-98 (Jan.) 1937.

18. Shwartzman, G.: Food Accessory Substances in Bacterial Growth, Proc. Soc. Exper. Biol. & Med. **22**: 7-9, 42-44 and 44-47, 1924. Thjotta, T., and Avery, O. T.: Studies on Bacterial Nutrition, J. Exper. Med. **34**:97-114, 1921. Shwartzman and Goldman.[17]

ditions, remained sterile during the four days of observation. The second, third and fourth samples of blood were cultured in the routine manner except that they were placed in an atmosphere of air containing approximately 3.5 per cent carbon dioxide.[19]. This atmosphere was obtained by placing a lighted candle in a glass jar fitted with a petrolatum-sealed cover. On the sixth day of incubation gram-negative and gram-positive spiral micro-organisms were observed on stained spreads from the 2 per cent dextrose–veal infusion broth and the 10 per cent tomato extract–veal infusion broth.

Because it became apparent from a study of the initial blood cultures that the micro-organism grew only in liquid mediums, the fifth and the subsequent specimens of blood taken for culture were placed only in 2 per cent dextrose–veal infusion broth and 10 per cent tomato extract–veal infusion broth and incubated in an atmosphere of 3.5 per cent carbon dioxide. The fifth specimen of blood, culture of which was sterile in all mediums, was taken after tryparsamide and neoarsphenamine had been administered over a period of eleven days. The arsenical therapy did not prove effective, however, for culture of the sixth specimen, taken twenty-four hours after an intravenous course of neoarsphenamine, yielded growth after only five days of incubation. Although culture of the seventh sample of blood, which was taken after mapharsen therapy, did not reveal S. minus, culture of subsequent samples yielded the organism. Culture of blood taken four days before death, however, gave negative results.

The micro-organism grew in the presence of carbon dioxide on the first transplant from the original blood culture flasks to a 2 per cent dextrose–veal infusion broth flask and a 10 per cent tomato extract–veal infusion broth flask. Three to 5 cc. of citrated human or rabbit blood was added to each of the flasks used for the transplant. Without the addition of blood, a second serial transplant yielded growth in these fluid mediums. After a third passage the organism failed to grow. By addition of citrated human blood to the 2 per cent dextrose–veal infusion broth and the 10 per cent tomato extract–veal infusion broth, the micro-organism was successfully carried for eighty generations, over a period of eleven months, before it finally died. When first isolated, the spirillum grew only in an atmosphere of 3.5 per cent carbon dioxide. After five months of transplantation, the micro-organism grew aerobically.

All attempts to subculture the micro-organism on Nichols, Novy and MacNeal agar, semisolid mediums, gelatin mediums, chocolate blood agar plates, plain agar plates and blood agar plates proved futile. This result agrees with the work of McDermott,[13] Robertson [8] and Steiner.[20]

Fig. 1.—Photomicrograph of a spread of material taken from the 10 per cent tomato extract-veal infusion broth containing the ninth blood culture after eight days of incubation, showing blood cells and S. minus, the organisms being of variable lengths. × 1,200; Gram stain.

Fig. 2.—Treponema recurrentis in the blood in a case of relapsing fever in man. × 1,400; Wright stain.

The morphologic features clearly differentiating this organism from S. minus are the greater length and a number of regular primary waves of notably wider amplitude.

19. Haynes, E.: The Importance of Culturing Hemolytic Streptococci Under Increased Carbon Dioxide Tension, Am. J. Clin. Path., Tech. Supp. **6**:55-56, 1942.

20. Steiner, W. R.: A Case of Rat-Bite Fever, Tr. Am. Clin. & Climatol. A. **46**:1-5, 1930.

Each of 4 mice received an intraperitoneal injection of 1 cc. of the second positive blood culture in the 10 per cent tomato extract–veal infusion broth. The animals remained in good condition for ten days. Peritoneal washings obtained by a capillary tube were examined by means of Gram-stained spreads. The spirillum was seen in the peritoneum on the fifth and seventh days after inoculation and disappeared from the peritoneum on the ninth day. On the fifth day 1 mouse was killed, and the spirillum was demonstrated on a spread of the heart's blood stained by the Gram method.

Morphologic Characteristics of S. minus: Dark field illumination of washings of the mouse peritoneum and of the blood culture suspension yielded identical pictures. Actively motile spirilla were seen moving rapidly across the field. The micro-organisms seemed rigid throughout their length; they moved forward in spiral fashion, while turning about on their longitudinal axis without bending.

taken by Dr. Gregory Shwartzman, illustrate the spirillum described.

Examination of Specimens from the Patient Other than the Blood: Cultures taken of material from the bases of the teeth and of the urine and the cerebrospinal fluid failed to reveal the presence of spirilla. The sediments of two specimens of cerebrospinal fluid, which had been centrifuged for ten minutes, were negative for spirilla on dark field examination and in spreads stained by the Gram method. A specimen of urine obtained when the patient's temperature was 102 F. and centrifuged ten minutes was also negative for the spirillum on dark field examination and in spreads stained by the Gram method.

Postmortem Observations: A spread of the blood taken from the heart at autopsy and stained by the Gram method revealed the spirilla. Crushings of the vegetations stained by the Gram method showed the spirilla clumped together in large masses.

Fig. 3.—Electron micrograph (Dr. Gregory Shwartzman). Magnification with the electron microscope, 8,000; photographic magnification, 3.75; total magnification, 30,000.

A centrifuged specimen of growth from a blood culture was washed in Locke-Ringer solution. A drop of a light suspension was dried on the surface of a collodion film. The dried film was quickly washed by the method of Anderson and Mudd and dried in the air before it was mounted on the target.

The complex structure of an undulate body is suggested by the photograph. In particular, the processes on the side and at the end of the main body are to be noted. The end process possibly is responsible for the appearance of the minus sign described by previous authors.

A Gram stain of the blood culture suspension and the peritoneal washings revealed gram-positive and gram-negative micro-organisms, of varying sizes and shapes. Generally, the length of the spirillum ranged from one-half to twice the diameter of an erythrocyte. The undulations were shallow and few, which imparted a slender, short appearance to the micro-organism. The ends of the spirilla were distinct. They were either straight or tapered, one end being longer than the other. The Giemsa stain revealed no new morphologic structures, the organism exhibiting a slender, beaded appearance with shallow undulations.

A photomicrograph of the S. minus and, for comparison, one of the Treponema recurrentis from a recent case in man, as well as an electron micrograph,

Serologic Studies.—Agglutination Test of Patient's Serum: Agglutination tests for the enteric group of organisms, Brucella abortus and Brucella melitensis, gave negative reactions. The agglutination test for heterophil antibodies gave positive results in 1:16 and 1:32 dilutions.

Serologic Reactions: In addition to the serologic tests performed at the Mount Sinai Hospital, similar tests were performed by another laboratory, by arrangement with Dr. Chargin, during the patient's stay at the hospital.

The paradoxic behavior of the serologic tests, as seen in tables 2 and 3, and the presence of an aortic lesion seemed to favor the assumption of a syphilitic infection. There was, however, no history of a primary lesion or

of a secondary eruption, and at autopsy the pathologic observations were negative for syphilis.

As seen in table 3, the positive reactions of the cerebrospinal fluid for syphilis reported from another hospital could not be confirmed at the Mount Sinai Hospital. This reaction must be regarded as a laboratory error or as a false positive reaction, which is known to occur with certain diseases (tumors and various forms of meningitis).

Postmortem Examination.—The body was that of a well developed, well nourished, tall, muscular white man. Over each hypothenar eminence was a round hemorrhagic area, 3 mm. in diameter.

Thorax: Each pleural cavity contained about 50 cc. of clear fluid.

Heart: The pericardial sac contained no excess fluid. The heart was moderately enlarged and weighed 460 Gm. The tract of outflow of the right ventricle and the trabeculae carneae were slightly thickened. The left auricle was slightly thickened; its appendages contained no thrombi. The free edge and the line of closure of the mitral valve were distinctly thickened, and the thickened free edge overhung the chordae tendineae in shelflike fashion. The chordae tendineae at their insertion into the anterior and the posterior leaflets of the mitral valve were also thickened and fused. An irregular row of vegetations was present along the line of closure and along the free edge of both mitral valves. These vegetations were pink and fleshy, and their diameters varied from 1 mm. to 0.5 cm. They extended downward onto the chordae tendineae. On the posterior leaflet, one vegetation presented a yellowish, cheesy, friable appearance. The aortic aspect of the anterior leaflet of the mitral valve presented near its center a large oval lesion, which measured 18 by 6 mm. A shallow ulceration occupied the center of the lesion, whereas the periphery was composed of a ring of verrucae surrounding the central ulceration, so that the whole lesion resembled an atoll. The peripheral verrucae were flat and fleshy, but at the lower edge they were larger and had the same yellowish, friable, cheesy appearance of some of the verrucae on the posterior leaflet of the mitral valve. The wall of the left ventricle was hypertrophied, and the trabeculae carneae were massive. The cusps of the aortic valve were moderately thickened, and their free edges appeared rolled. This was particularly evident in the posterior cusp, where thickening of the free edge had produced shortening of the cusp. There was slight fusion at the commissures between the left and the right anterior cusp and between the posterior and the left anterior cusp. It cannot be said, however, that there existed a real anatomic insufficiency of the aortic valve. Over the nodule of Arantius of the right anterior cusp was a ragged, fleshy group of vegetations the size of a pinhead. The myocardium was pale red. The coronary arteries were widely patent and showed no sclerosis. The ostium of the right coronary artery was smaller than usual. There were two minute accessory coronary ostiums. The aorta was smooth and elastic. There was significant atheromatous flecking of the coronary sinuses.

Lungs: The lungs weighed 1,600 Gm. and were large and heavy. The pleural surfaces were smooth and glistening. The trachea and bronchi oozed large quantities of sanguineous foam. The cut surfaces were moist and contained a good deal of blood. There were no areas of consolidation. The pulmonary vessels were normal.

Liver: The liver was large and weighed 2,400 Gm. Its surface was smooth and glistening and showed brownish red to brown mottling. On section it had the appearance of chronic passive congestion, with irregular distribution of blood. The gallbladder, the bile ducts, the portal vein and the hepatic artery were normal.

Pancreas: The pancreas was moderately firm. On section it appeared normal but was congested and tawny. The pancreatic ducts were not dilated.

Spleen: The spleen was large, flabby and rather long. It weighed 700 Gm. The surface was smooth, glistening and gray, except for one large, slightly bulging area near the lower pole, which had a dark red and yellowish mottling. This area evidently represented a large infarct, which on section appeared wedge shaped, necrotic and yellowish. The spleen was extremely pulpy when sectioned elsewhere. The pulp was purplish and oozed from the cut surface. After the purplish, diffluent pulp was removed with a sponge, the spleen presented an unusual appearance. It was studded with innumerable whitish nodules, 2 to 3 mm. in size, many of which appeared confluent. The nodules were much larger than the usual follicles, and on close examination it was suspected that the central portions of many

TABLE 2.—*Serologic Data on the Blood*

Examination	Wassermann Test	Hinton Test	Kahn Diagnostic Test	Kahn Verification Test	Kline Diagnostic Test	Kline Exclusion Test	Mazzini Test
Draft board	—	..	...	..	...	...	...
Another hospital, 2/42	4+	+	...	..	...	...	...
Mount Sinai Hospital, 3/30	4+	..	3+	..	...	...	...
4/ 9	4+	..	3+	..	...	...	...
5/13	4+	..	3+	..	...	...	...
6/16	4+	..	1+	..	...	...	...
Another laboratory, 5/2	Anticomplementary	..	...	..	3+	4+	2+
5/7	Anticomplementary	..	4+ 40 units	Syphilitic type of verification reaction	3+	4+	3+

TABLE 3.—*Data on the Spinal Fluid in a Case of Rat Bite Fever*

Examination	Wassermann Reaction	Colloidal Gold Curve	Reaction for Globulin
Another hospital			
First puncture	4+	..	3+
Second puncture	3+	Paretic	—
Mount Sinai Hospital, 4/7.	—	—	±

whitish nodules were somewhat grayish and more opaque, an appearance suggestive of the original follicles. In the area adjacent to the infarct the red pulp was much firmer and was deeply congested, and the true follicles were more evident. These follicles were smaller than the white nodules already described. The splenic artery and vein were normal.

Gastrointestinal Tract: Except for congestion, the esophagus, stomach and intestinal tract presented nothing unusual. In the midportion of the mesentery of the small intestine, a large nodule, of hazelnut size, was observed along the course of one of the mesenteric arteries. Section of the nodule exposed a saccular aneurysm, with a thin wall on one side and a crescentic, lamellated wall on the opposite side. The involved vessel was easily probed, and no occlusion proximal or distal to the aneurysm could be demonstrated. The small intestine supplied by this altered mesenteric artery presented no gross abnormality.

Genitourinary Tract: The kidneys were similar in size and appearance and together weighed 360 Gm. The capsules stripped with ease, with exposure of a smooth, reddish surface. No petechiae or hemorrhages were seen. A few scattered, small, flat, stellate dark depressions were noted in the cortex. Several small round, yellowish white areas, 2 to 3 mm. in diameter, were discerned on the surface. These extended into the center for a distance of 2 to 3 mm. On section the architecture of the kidney was not unusual. The cortex was of normal width. The glomeruli were not clear. The medullary markings were normal. The renal pelves and ureters were normal. The urinary bladder, prostate, seminal vesicles, testes and epididymides appeared grossly normal.

Adrenal Glands: The adrenals were normal in size and shape. The yellowish cortex was congested.

Bone: A lumbar vertebra showed a moist, red, finely spongy marrow.

Microscopic Examination.—Heart: A Gram stain of a section through a vegetation on the mitral valve showed granular, rod-shaped and comma-shaped coccoid bodies (the latter being considerably smaller than ordinary cocci). This granular material was gram-positive. The base of the vegetation showed organization, as seen in cases of subacute endocarditis due to Streptococcus viridans. Section of the myocardium of the left ventricle (hematoxylin-eosin stain) demonstrated numerous ill defined, fibrotic and hyalinized perivascular areas. A few scattered myocardial areas presented fully developed Aschoff bodies.

Lungs: Edema and congestion were pronounced; occasional heart failure cells were present.

Liver: Edema was marked. There were prominent Kupffer cells and slight lymphocytic infiltration in the periportal areas.

Spleen: Examination revealed acute infectious splenitis, with multiple foci of small infarcts.

Pancreas: Scattered foci of lymphocytic infiltration occurred within the acini, with atrophy of the acinar tissue.

Adrenals: Severe congestion and an acute mycotic aneurysm of a small artery of the adrenal capsule were noted.

Kidneys: Sporadic acute focal embolic glomerular lesions were present, some of which were fibrotic. Scattered glomeruli were completely fibrosed. These altered glomeruli were often surrounded by zones of lymphocytes. Small foci of abscess-like lesions were noted in the cortex.

Mesenteric Artery: A mycotic aneurysm with organizing thrombus was noted.

Summary of Anatomic Observations.—The anatomic changes were: subacute bacterial endocarditis of the mitral and aortic valves; rheumatic heart disease; chronic interstitial valvulitis of the aortic and mitral valves; rheumatic myocarditis (Aschoff nodules); mycotic aneurysm of a branch of the superior mesenteric artery; hypertrophy of the right and left ventricles (moderate); infectious splenitis, splenomegaly and subacute splenic infarct; pulmonary congestion and edema, and chronic passive congestion of the liver.

COMMENT

The clinical course was similar to that usually encountered in cases of subacute bacterial endocarditis. The classic features of the latter condition observed in this case were low grade fever with occasional increases in temperature, endocardial murmurs, splenomegaly, multiple visceral and subcutaneous embolization, microscopic hematuria, petechiae, Osler and Janeway lesions and subarachnoid hemorrhage as a terminal event. That the endocarditis was subacute was clearly established by its long duration, i. e., an interval of nineteen weeks from the earliest febrile episode to the termination of the illness.

The isolation of S. minus from the blood culture led to considerable speculation as to the cause and pathogenesis of the endocarditis. At first, there was doubt as to the etiologic role of the micro-organism identified as S. minus, since there was no history of rat bite. On closer investigation it was found that the food ingested by the patient at the water front was exposed to rats and wild cats. The patient also had direct contact with alley cats, a fact which might be significant since a case of rat bite fever following a cat bite [21] has been reported.

It is of interest at this point to mention Mooser's [22] work, which revealed on anatomic grounds that the pathway of transmission is not necessarily through contact with the blood of the infected rat. According to this author, the invariable presence of keratitis in the afflicted animals may be responsible for the following method of spread of the disease:

> The spiral micro-organism passes through the lacrimal channel into the nasal cavity and hence may enter the mouth, though its presence there is not absolutely necessary for transmission through bites. The upper lip of the rat is cleft and since the biting animal touches the bitten object with the nose, the organism may enter the wound from this point.

In our case it is assumed that the skin or the gastrointestinal tract was the possible portal of

21. Mock, H. E., and Morrow, A. R.: Rat-Bite Fever Transmitted by Cat-Bite, Illinois M. J. **61**:67-70, 1932.

22. Mooser, H.: Experimental Studies with a Spiral Organism Found in a Wild Rat, J. Exper. Med. **39**: 589-602, 1924.

entry. That the micro-organism isolated was identical with that of rat bite fever was confirmed by its morphologic structure, its cultural characteristics and its power to invade mice. The etiologic significance was clearly established by six repeatedly positive blood cultures during a period of two months, the absence of any other organisms in the blood cultures and the demonstration of the organism in the crushings of the vegetations removed post mortem. The positive serologic reactions provided additional indirect evidence that the micro-organism causing the endocarditis in this case was S. minus.[5]

It is doubtful whether this micro-organism bears any resemblance to the spirillum isolated from the blood in Lamb and Paton's [7] case of subacute endocarditis caused by a spirillum. The striking biologic differences of the two spirilla are evident from the following summary:

	Lamb and Paton's Case	Our Case
Blood culture	Organism grew aerobically; growth appeared in 5-6 days	Organism grew in 3.5% carbon dioxide; growth appeared in 5-9 days
Subcultures	Successive transplants grew in 24 hours	Successive transplants required human citrated blood and 3.5% carbon dioxide; growth appeared in 5-6 days
Serologic reactions	Wassermann reaction negative	Wassermann, Kahn and Kline reactions positive

The cultural dissimilarity of the micro-organisms, as well as the difference in their serologic reactions in man, offers supporting evidence that the two strains are quite different.

The absence of a cutaneous rash does not mitigate against the assumption that rat bite fever, rather than the endocarditis, was the initial illness, the subacute endocarditis supervening at a later stage. The early history was vague, and the type of rash invariably observed in the early exacerbations of rat bite fever could well have been mild enough to be overlooked. Certainly even the periodicity of the fever suggests the trend toward "relapsing" elevations of temperature described in cases of rat bite fever.

The presence of lesions in the heart gave support to the clinical impression that the patient was suffering from chronic rheumatic disease of the mitral and aortic values, on which was superimposed subacute verrucous endocarditis due to infection with a spirillum. The absence of clinical and roentgengraphic evidence of significant cardiac enlargement, as well as the absence of evidence of a murmur of aortic insufficiency during examination by the draft board one year before, can be satisfactorily explained on the basis of the postmortem observations. Careful examination of the aortic valves revealed fusion of the commissures of the cusps, but no significant aortic incompetence could be demonstrated anatomically. The hemodynamic evidence of aortic insufficiency probably appeared later, as a result of the vegetations on the aortic valves due to infection with the spirillum, which must eventually have interfered with the competent closure of the ostium of the valves during diastole. The patient did not live long enough, however, to manifest the classic enlargement of the left ventricle associated with disease of the aortic valves.

Mycotic aneurysms of the type observed in segments of the superior mesenteric and the adrenal arteries are frequently encountered with bacterial endocarditis. A similar lesion was undoubtedly present in a cerebral artery and led to the terminal subarachnoid hemorrhage.

There was neither gross nor microscopic postmortem evidence to substantiate a clinical or a serologic diagnosis of syphilis. Although, from a theoretic standpoint, anatomic corroboration is unnecessary for the diagnosis of syphilis in a patient of the age of this man, the negative evidence at autopsy and the fact that a high percentage of false positive serologic reactions have been reported in cases of infections with the spirillum [8] should serve as evidence sufficient to refute the diagnosis of a coexisting hidden syphilitic infection.

Arsenicals were employed without success. Despite their therapeutic efficiency in cases of rat bite fever, they exerted little, if any, effect on the growth and dissemination of the spirilla in this case of verrucous endocarditis. The patient received a total of 1.5 Gm. of neoarsphenamine. A negative blood culture for the spirillum was obtained after completion of neoarsphenamine therapy and another after administration of mapharsen was finished. A third negative culture was obtained four days before the patient's death, even though the crushings from the valves, obtained post mortem showed an abundance of the micro-organisms. Negative blood cultures are frequently observed in cases of subacute bacterial endocarditis, and their occurrence in this case must also be regarded as accidental rather than as a temporary effect of the arsenicals employed.

This case emphasizes the importance not only of cautious interpretation of serologic tests but of accurate anatomic localization of existing valvular murmurs. It is true that syphilis may

occur at any age, but the diagnosis of acquired aortic insufficiency of syphilitic origin at the patient's age is open to question. It was the unfortunate combination of a false positive Wassermann reaction and an audible murmur of aortic insufficiency that led able clinicians to ignore a coexisting loud blowing apical systolic murmur of mitral insufficiency, which, if it had been evaluated properly, would have led to question of the validity of the diagnosis of syphilis. In this instance, the patient would have been spared much unhappiness and embarrassment if he had not erroneously been stigmatized as syphilitic.

SUMMARY

In a case of subacute endocarditis due to S. minus, the etiologic micro-organism of rat bite fever was isolated six times from the blood in dextrose and tomato bouillon and grown in an atmosphere of 3.5 per cent carbon dioxide. Its relation to the causative organism of rat bite fever was established by its morphologic characteristics, its pathogenicity and serologic effects in man and its invasiveness for mice.

Despite the unusual micro-organism, the clinical course and the changes observed at autopsy were strikingly similar to those observed in cases of the common form of subacute bacterial endocarditis due to Str. viridans.

A comparison of the spirillum causing the subacute endocarditis in Lamb and Paton's case with the spirillum in the case presented here reveals striking differences in their biologic and cultural characteristics, as well as in their serologic effects in man.

Mount Sinai Hospital.

SALMONELLA CHOLERAE SUIS MENINGITIS

REPORT OF A CASE AND REVIEW OF THE LITERATURE ON SALMONELLA MENINGITIS

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BUFFALO

In contradistinction to typhoid, the present day knowledge of paratyphoid infections of man is as yet incomplete, although important advances in this field have been made during the last few years. The identification of the various members of the Salmonella group presents difficulties far greater than those encountered in the recognition of the typhoid bacillus. The genus Salmonella is comprised of many different species and types. As a matter of fact, more than one hundred species have been described in the past as pathogens for human beings or animals or both. Special diagnostic antiserums are required to establish species or type identity. To add to the difficulty, the members of the Salmonella group are responsible for a variety of clinical syndromes. The diseases may be classified conveniently into three large groups: (1) paratyphoid, (2) gastroenteritis and (3) pyogenic infections. To the latter group belong such syndromes as septicemia, peritonitis, osteomyelitis, pharyngitis, otitis, abscesses, empyema, pyelitis, arthritis, cholecystitis, appendicitis, meningitis and others.

Purulent meningitis caused by members of the Salmonella group is not a common disease, although it is not so rare as is often believed. In 1940 Guerra, Peluffo and Aleppo,[1] in an excellent article, reviewed the literature on Salmonella meningitis. They collected 56 cases. Since that time additional cases have been reported. Salmonella cholerae suis accounts for only a small fraction of meningitis, although this particular organism is not uncommonly found as the cause of other diseases. Only 3 definitely established and well described cases of S. cholerae suis meningitis could be found in the literature. It was decided therefore to present the clinical, bacteriologic and immunologic observations of such a case and review the status of the Salmonella meningitis problem with particular reference to the incidence of the various species in this malady.

From the Children's Hospital and the Department of Bacteriology and Immunology, University of Buffalo, School of Medicine.

1. Guerra, A. R.; Peluffo, E., and Aleppo, P. L.: Localizaciones extraintestinales, en el niño, de las bacterias productoras de enteritis infantiles, in Bonaba, J., and others: Estudios sobre la etiologaía infecciosa de las diarreas infantiles, Montevideo, Editorial Médica J. Garcia Morales, 1940, pp. 91-130.

REPORT OF CASE

P. T., a white girl 3 years and 11 months of age, was admitted to the Children's Hospital (service of Dr. Norman C. Bender) on Sept. 22, 1943. The history revealed that the child was delivered instrumentally after seventy-two hours of labor. The birth weight was 8 pounds 8 ounces (3,856 Gm.). After birth extreme hydrocephalus developed, and the child had been blind. She sat alone at 12 months, walked at 30 months and talked at 2 years of age. Her mental development was retarded. There was no history of diarrhea or of other illness of consequence.

The physical examination on admission revealed the following facts: The child screamed almost continuously and appeared to be delirious. The temperature was 103 F.; the pulse rate was 140 per minute and the respiratory rate 40 per minute. The head was extremely large. Its circumference was 25.5 inches (64.8 cm.) and that of the chest 21.5 inches (54.6 cm.). The anterior fontanel was closed. Nystagmus was present. The pupils were constricted and reacted only sluggishly to light. There was definite rigidity of the neck. The pharynx was slightly injected. The spleen and liver apparently were not enlarged. The Kernig sign was positive bilaterally; the Babinski sign was absent, and the deep reflexes were normal. There were no petechiae present. Roentgen ray examination of the chest revealed no abnormal conditions.

A culture of blood showed the presence of a paratyphoid bacillus. Its characteristics will be described later.

Examination of the blood showed a hemoglobin content of 12 Gm. and 3,700,000 red cells and 10,500 white cells per cubic millimeter, of which 54 per cent were polymorphonuclear cells, 40 per cent juvenile cells and 6 per cent lymphocytes.

A lumbar puncture was done on the day of admission. Approximately 20 cc. of slightly cloudy fluid was obtained. The pressure was greatly increased (above 500 mm. of water). This spinal fluid contained 119 leukocytes per cubic millimeter, of which 92 per cent were polymorphonuclear cells and 8 per cent lymphocytes. Globulin was present, and dextrose was absent. The microscopic examination revealed the presence of numerous gram-negative bacilli, subsequently identified as paratyphoid organisms. A second lumbar puncture was performed on the same day. The number of leukocytes had increased to 1,620 per cubic millimeter; dextrose was still absent, and globulin was present. The spinal fluid contained many gram-negative bacilli.

Examination of the feces failed to reveal paratyphoid bacilli, in spite of the fact that five different culture

mediums (Endo, MacConkey, SS, desoxycholate-citrate and bismuth sulfite agar) were used.

The serum of the patient was examined for the presence of specific agglutinins. The strain isolated from the spinal fluid was used as the antigen. Agglutinins were not present in dilutions of serum ranging from 1:10 to 1:1,000.

Sulfadiazine was given, 2 Gm. immediately after admission and 1 Gm. every four hours thereafter. In spite of this treatment, the child died the following day.

In order to determine the possible source of the infection, three members of the immediate family (father, mother and brother) were examined. Their feces did not contain paratyphoid bacilli, and agglutinins against the patient's strain could not be demonstrated in their serums.

The results of bacteriologic study were as follows: The blood culture contained innumerable colonies (per cubic centimeter) of gram-negative bacilli which had biochemical and antigenic characteristics identical with those of the strain isolated from the spinal fluid. The organism was motile and grew well on simple artificial mediums. It produced acid and gas from dextrose, maltose, mannitol, dulcitol, xylose, rhamnose and sorbitol. It failed to attack lactose, sucrose and salicin. The strain was tentatively identified as a member of the Salmonella group and was sent for further study to the New York Salmonella Center (Dr. Erich Seligmann, director). There it was identified as S. cholerae suis.

The postmortem examination was performed by Dr. Kornel L. Terplan. The significant conditions observed were the following:

Acute seropurulent meningitis. Very distinct, old hemorrhagic gliosis of the right cerebellar hemisphere, with firm membranous obliteration of the foramens of Luschka. Pronounced inner hydrocephalus. Massive recent suffusions in the leptomeninges in the right parieto-occipital area.

Acute, desquamative and moderately hemorrhagic enteritis, most severe in the duodenum and the lower portion of the ileum.

Scattered suffusions in the skin, especially of both extremities.

COMMENT

An attempt has been made to review cases of Salmonella meningitis described during the past twenty years and to present the incidence of the different species and types of Salmonella organisms encountered in this malady. In addition to the data compiled from 56 cases by Guerra and associates,[1] 22 case reports have been collected. Indubitably, other cases have escaped detection. It seemed of no value to consider cases described many years ago, since no reliable information could be gained with respect to the incidence of the different Salmonella types. Furthermore, it must be admitted that in some of these cases a complete antigenic analysis of the respective strains was not carried out. Nevertheless, the figures shown in table 1 give an approximate picture of the incidence in meningitis of the various types of organisms of the paratyphoid group. There are several facts worthy of comment. In the first place, it may be seen that twelve different species or types have been encountered in the past as causative agents in this disease. These represent only a fraction of the species known to be pathogenic to man. It seems reasonable to assume, therefore, that in the future other species may be found in Salmonella meningitis. Secondly, it is interesting to note that not a single case of paratyphoid A bacillus meningitis is included in this group. However, Facatselli [2] mentioned by reference that this organism has been found in meningitis. Members of group B of the genus Salmonella account for 26, or one third, of all cases. Only 5 cases of meningitis were caused by S. cholerae suis, the sole representative of group C. More than half of all instances of Salmonella meningitis were due to members of group D. Group E is represented by Salmonella sp. (London type) in a single case.

TABLE 1.—*Incidence of Types of Salmonella in Meningitis*

Group	Type or Species	Synonym of Species	Number of Cases of Meningitis	References
A	S. paratyphi	.....	0	
B	S. schottmuelleri	S. paratyphi B	8	Patterson,[11] Schmidt,[14] Jundell,[15] Leenhardt et al.,[23] Caselli and Teobaldo,[24] Gordon, H., and Kennedy, J. A.: Am. J. Clin. Path. **8**: 170, 1938; Bahrenburg, J. H., and Ecker, E. E.: J. Infect. Dis. **60**: 81, 1937.
	S. typhimurium	S. aertryke S. enteritidis Breslau	17	Guerra et al.[1] Aballi et al.[16]
	S. Sandiego	.....	1	Bray and Meredith.[19]
C	S. cholerae suis	S. suipestifer	5	Guerra et al.[1], Boycott and McNee,[4] Ravitch and Washington,[5] Kuttner and Zepp.[6]
D	S. enteritidis	S. enteritidis Gaertner	34	Guerra et al.,[1] Crozier,[13] Wengeler, F.: Med. Klin. **36**: 1217, 1940; Opitz,[21] Hayasaka,[25] Meyer-Rohn, J.: Deutsche med. Wchnschr. **66**: 1193, 1940; Rieper, P.: Virchows Arch. f. path. Anat. **289**: 301, 1933.
	S. sp. (Panama type)	.....	1	Guerra et al.[1]
	S. enteritidis (variety Dublin)	.....	5	Guerra et al.[1]
	S. enteritidis (variety Kiel)	.....	1	Guerra et al.[1]
	S. sp. (Eastbourne type)	.....	2	Guerra et al.,[1] Valledor et al.[26]
	S. enteritidis (variety Jena)	.....	3	Wengeler, F.: Med. Klin. **36**: 1217, 1940.
E	S. Sp. (London type)	.....	1	Wilsdon and Gibson.[18]

2. Facatselli, N.: Les manifestations méningées et les méningites d'origine éberthienne ou para-typhique, Arch. de méd. d. enf. **42**:615-626 (Oct.) 1939.

Naturally, the question arises whether or not the incidence of these Salmonella types in meningitis is comparable to that in other Salmonella infections. Bornstein,[3] in his excellent review on the state of the Salmonella problem, reported on the type distribution among five hundred strains of Salmonella isolated from human beings in North America and Cuba during the years 1939 to 1941. Group A accounted for 2 per cent, group B for 47 per cent, group C for 38 per cent, group D for 7.5 per cent and group E for 5.5 per cent. It is not possible to compare the incidence of the different Salmonella types in these two series. Bornstein's figures were obtained over a three year period and included strains isolated in North America and Cuba only, whereas the figures for Salmonella meningitis cover a period of many years and include species recovered in Europe and South America as well. Nonetheless, it is impressive to note that group C is encountered in a lower percentage and group D in a higher percentage in meningitis than in Salmonella infections in general.

In this connection it is important to stress that all strains of Salmonella organisms encountered as causative agents in meningitis—and in other infections as well—should be adequately identified. Since many laboratories are not equipped to carry out the antigenic analysis of these strains, it seems advisable to send subcultures to Salmonella centers. Only then will it be possible to obtain an accurate picture of the incidence of the different Salmonella species in infections of man.

Among 78 cases of Salmonella meningitis reported in the literature, only 4 were due to S. cholerae suis, also referred to as Salmonella suipestifer. An additional case has been reported in this study. Of the 4 cases previously published, only 2 are recorded in detail, 1 by Boycott and McNee[4] and the other by Ravitch and Washington.[5] The case of Kuttner and Zepp[6] is only briefly mentioned in their article. The patient was comatose on admission to the Baltimore City Hospital and died shortly afterward. No adequate history could be obtained. A diagnosis of chronic meningitis was made. The strain isolated from the spinal fluid proved to be a monophasic suipestifer, group 2. No data are available on the clinical aspects of the disease in the case of Materna and Januschke.[7] It is true that other cases of S. cholerae suis meningitis have been described in the literature. However, in the case of Lyon and Folsom,[8] for instance, this diagnosis was not adequately substantiated. The organism isolated by these authors was described as a bacillus producing acid and gas from certain carbohydrates. On the other hand, the subculture of this organism was identified at the Harriet Lane Home and at the National Institute of Health as an atypical influenza bacillus. This discrepancy in the results is difficult to explain unless one assumes that two different microorganisms were involved. If this is the case, either one of the organisms was a contaminant or the patient was suffering from a mixed infection. But even if the gas-producing organism was actually the causative agent of the disease (as a primary incitant or secondary invader), one cannot accept this case as an instance of S. suipestifer infection, since the strain was not adequately investigated serologically.

Furthermore, a number of cases of meningitis were described during and after World War I as having been caused by bacilli of the Glässer-Voldagsen group and by paratyphoid bacillus N (Erzindjan), respectively (Hesse,[9] Neukirch[10]). According to the Kauffmann-White scheme, Neukirch's Bacillus Erzindjan is either Salmonella paratyphi C, Salmonella moscow or Salmonella enteritidis. The Glässer bacillus is identical with Salmonella typhi suis, and the Voldagsen variety is its monophasic nonspecific variety (Bornstein, personal communication). At any rate, these cases cannot be considered as instances of S. cholerae suis meningitis.

The pertinent features of the 5 cases of Salmonella cholerae suis meningitis are summarized in table 2.

The diagnosis of this infection presents certain difficulties. In the case reported here the micro-

3. Bornstein, S.: The State of the Salmonella Problem, J. Immunol. **46**:439-496 (June) 1943.

4. Boycott, J., and McNee, J. W.: Human Infection with American Hog-Cholera Bacillus, Lancet **2**:741-742 (Sept. 26) 1936.

5. Ravitch, M. M., and Washington, J. A.: Suipestifer Septicemia and Meningitis Complicating Meningococcic Septicemia and Meningococcic Meningitis, J. A. M. A. **109**:1122-1123 (Oct. 2) 1937.

6. Kuttner, A. G., and Zepp, H. D.: Paratyphoid-Like Fever in Children Due to the Salmonella Suipestifer Group, Bull. Johns Hopkins Hosp. **51**:373-387 (Dec.) 1932.

7. Materna, A., and Januschke, E.: Ein Beitrag zu der Frage der ätiologischen Beziehungen zwischen der bazillären Schweinepest und dem Paratyphus B des Menschen, Ztschr. f. Fleisch- u. Milchhyg. **35**:298-300 (July 1) 1924-1925.

8. Lyon, G. M., and Folsom, T. G.: Meningitis Due to Salmonella Suipestifer: Case Report, West Virginia M. J. **37**:249-255 (June) 1941.

9. Hesse, E.: Zur Kenntnis der chirurgischen Komplikationen und Nachkrankeiten des Fleckfiebers, Rückfallfibers und des Paratyphus N. (Erzindjan), einer Mischinfektion des Recurrens, Arch. f. klin. Chir. **128**: 739-814, 1924.

10. Neukirch, P.: Ueber menschliche Erkrankungen durch Bazillen der Glässer-Voldagsengruppe in der Türkei, Ztschr. f. Hyg. u. Infektionskr. **85**:103-145, 1918.

scopic examination of the spinal fluid revealed numerous gram-negative bacilli. Haemophilus influenzae meningitis was therefore considered. Precipitation tests with the supernatant liquid of the spinal fluid and type-specific anti–H. influenzae serums yielded entirely negative results. Thus, it became unlikely that the patient was suffering from this particular infection. The cultural findings supported this assumption. The organism grew profusely in infusion broth and on Endo agar. Since there was no evidence that the organism produced acid from lactose (as indicated by the appearance of the colonies on Endo agar), a tentative diagnosis of typhoid or paratyphoid bacillus meningitis was made. Further biochemical and serologic examinations revealed that the bacillus belonged to the Salmonella group. It was identified as S. cholerae suis. The micro-organism isolated from the blood of the patient proved to be identical with that recovered from the spinal fluid.

TABLE 2.—*Salmonella Cholerae Suis Meningitis*

	Boycott and McNee	Cases of Ravitch and Washington	Kuttner and Zepp	Materna and Januschke	Neter
Age (years)	35	4	.....	.....	4
Race	.....	Negro	.....	.....	White
Sex	Female	Female	.....	.....	Female
Blood culture *	Positive	Positive	.....	.....	Positive
Feces culture *	.....	Negative	.....	.....	Negative
Urine culture *	.....	Negative	.....	.....	.....
Widal test †	.....	Positive (1:2,560)	.....	.....	Negative
Previous diseases	None	Meningococcic meningitis and bacteremia	.....	.....	Hydrocephalus
Concomitant diseases	None	Meningococcic meningitis and bacteremia	.....	Malaria	None
Therapy	.....	Antimeningococcus serum	.....	.....	Sulfadiazine
Outcome	Fatal	Recovered	Fatal	Fatal	Fatal
Incidence of Salmonella infection among family	.....	.....	.....	.....	Stool cultures and Widal tests on father, mother and brother: negative

* Examined for presence of S. cholerae suis.
† Examined for antibodies to S. cholerae suis.

The pathogenesis of Salmonella meningitis is not completely understood at the present time. In some of the cases the disease has been considered as primary; in others, as secondary. As far as the latter group is concerned, meningitis has been reported as a complication of paratyphoid, for example, by Patterson.[11] In Patterson's case the results of stool culture and of the Widal test were positive six days preceding the appearance of the first signs of the meningeal infection. The patient observed by Smith[12] suffered from Gaertner bacillus enteritis for two weeks before meningitis developed.

In the majority of cases the portal of entry remains unknown. It is likely that the organism invades the blood stream from the intestinal tract or, in the opinion of the Uruguayan investigators, from the pharynx. In the case of my patient, examination of the feces failed to reveal the presence of paratyphoid bacilli. Moreover, the patient did not have diarrhea. On the other hand, it must be pointed out that the postmortem examination revealed definite inflammatory lesions in the intestinal tract. In cases with bacteremia the possibility should be considered that the intestinal lesions may be a sequela of, rather than the primary focus leading to, invasion of the blood stream.

With respect to the origin of the infection, it is possible either that Salmonella meningitis develops in carriers or that the organism originates from the outside. Crozier[13] reported an infection with Salmonella supposedly milk borne or water borne. In another instance the mother of a 6 week old infant who died from paratyphoid B bacillus meningitis harbored the identical micro-organism (Schmidt[14]). A similar experience was reported by Jundell.[15] An investigation was carried out to determine whether the infection of the patient reported here originated from members of the immediate family. Examination of the feces and blood serum of the child's father, mother and brother, however, yielded entirely negative results.

Of particular interest is the occurrence of epidemic outbreaks of Salmonella infections, including meningitis, in the newborn. Aballí and associates[16] reported the cases of 12 infants infected with Salmonella aertrycke. Apparently the central nervous system was involved in all cases. The spinal fluid was either xanthochromic, serous or frankly purulent. From the report it is difficult to determine how many of these infants actually suffered from Salmonella meningitis. However, it is probable that bacterial meningitis was present in 9 of these

11. Patterson, W. H.: Paratyphoid B Meningitis: Two Cases Which Recovered, Lancet **1**:678-679 (June 6) 1942.

12. Smith, J.: Gaertner Meningitis Complicating Gaertner Enteritis, Lancet **2**:705 (Oct. 1) 1921.

13. Crozier, T. H.: Meningitis Due to Bact. Enteritidis (Gaertner), Ulster M. J. **7**:261-262 (Oct.) 1938.

14. Schmidt, B.: Paratyphus-B-Meningitis bei einem Säugling, Klin. Wchnschr. **17**:303-304 (Feb. 26) 1938.

15. Jundell, I.: A Case of Paratyphoid Meningitis, Acta pædiat. **14**:229-231, 1932.

16. Aballí, A. A.; Falcon, S.; Sala Panisello, F.; Curbelo, A., and Martínez Cruz, J. A.: Salmonelosis del recién nacido, Bol. Soc. cubana de pediat. **9**:123-160 (April) 1937.

patients. Guthrie and Montgomery [17] reported an epidemic outbreak of Salmonella enteritis. In all, 28 cases were observed. Of these, 11 were cases of purulent meningitis. The majority of these Salmonella infections occurred in a nursery of a maternity hospital; the infection in all likelihood was milk borne. The source of the epidemic could not be traced. One additional case of purulent meningitis caused by S. enteritidis, variety Dublin, was observed by these authors.

The Widal test is of limited value in the diagnosis of Salmonella meningitis, at least as far as its early recognition is concerned. In the case here reported agglutinins were not present in the patient's serum, probably because of the short duration of the disease. In other instances, however, the Widal reaction became positive during the course of the illness, for example, in the cases reported by Wilsdon and Gibson,[18] Patterson,[11] Ravitch and Washington [5] and others. It is interesting to note that in the case observed by Ravitch and Washington [5] the agglutinin titer was only 1:80 on the twenty-first day of the illness; it increased to 1:320 on the thirty-third day and to 1:2,560 on the forty-second day.

The question arises: Why do Salmonella organisms localize in the meninges of patients with Salmonella bacteremia? Although no definite answer can as yet be given, it is evident that in some cases at least certain conditions create a locus minoris resistentiae. In the case reported in this study, for instance, meningitis developed in a child who had been hydrocephalic since birth. A similar observation was made by Bray and Meredith.[19] Guthrie and Anderson,[20] and Opitz, [21] as well as Ravitch and Washington,[5] described cases in which paratyphoid bacillus meningitis complicated meningococcic meningitis.

Aside from the problem of the localization of the organism in the meninges, it seems likely that Salmonella bacteremia and meningitis develop in persons with diminished resistance, particularly after other infections. This aspect of the problem has recently been discussed (Neter [22]). In the case of Leenhardt, Boucomont, Labraque-Bordenave and Barnay [23] paratyphoid B bacillus meningitis followed otitis media. Caselli and Teobaldo [24] observed a newly born child in whom an infection of the urinary tract, caused by Bacillus coli, preceded paratyphoid B bacillus meningitis. Finally, attention should be called to the observations of Hayasaka,[25] who reported on Gaertner bacillus meningitis developing in patients infected with malaria for therapeutic purposes. The patient of Materna and Januschke [7] with S. suipestifer meningitis suffered also from malaria.

The prognosis of Salmonella meningitis is still poor. Only a few cases with recoveries have been reported in the literature, for example, by Ravitch and Washington,[5] Valledor, García Pérez and Pedrera,[26] Patterson,[11] Storey [27] and Katsampes and Bradford.[28] As far as S. cholerae suis meningitis is concerned, Ravitch and Washington [5] described the only instance in which recovery took place. Treatment with sulfadiazine proved to be ineffective in the case of S. cholerae suis meningitis and bacteremia presented here. Of course, no conclusions with respect to the efficacy of sulfonamide compounds can as yet be drawn, since recovery may occur without the use of chemotherapy (Ravitch and Washington [5]). Finally, it may be pointed out that the sulfonamide compounds are not equally effective toward all species and types of the genus Salmonella.

Dr. Erich Seligmann identified the organism, and Dr. Norman C. Bender supplied the clinical data of this case.

219 Bryant Street.

17. Guthrie, K. J., and Montgomery, G. L.: Infections with Bacterium Enteritidis in Infancy with the Triad of Enteritis, Cholecystitis and Meningitis, J. Path. & Bact. **49**:393-409 (Sept.) 1939.

18. Wilsdon, K. F., and Gibson, A.: Meningitis Due to Salmonella London, Lancet **1**:665-666 (May 24) 1941.

19. Bray, W. E., and Meredith, J. M.: Fatal Salmonella Intracranial Infection in an Infant, J. Lab. & Clin. Med. **28**:152-156 (Nov.) 1942.

20. Guthrie, K. J., and Anderson, T.: Double Infection of the Meninges with Meningococcus and Gaertner's Bacillus, Brit. M. J. **1**:193-194 (Feb. 8) 1941.

21. Opitz, H.: Zwei Fälle von Mischinfektion mit Bacillus enteritidis Gaertner, Monatschr. f. Kinderh. **15**: 383-388, 1919.

22. Neter, E.: Salmonella Cholerae Suis (Weldin) Bacteremia, Am. J. Dis. Child. **64**:255-261 (Aug.) 1942.

23. Leenhardt, E.; Boucomont, J.; Labraque-Bordenave, and Barnay: Méningite à paratyphique B chez un nourrisson, Arch. Soc. d. sc. méd. et biol. de Montpellier **18**:94-99 (Feb.) 1937.

24. Caselli, E. G., and Teobaldo, C. T.: Meningitis a bacilo paratífico B en un lactante, Arch. argent. de pediat. **10**:416-423 (Oct.) 1939.

25. Hayasaka, C.: Im Verlauf einer Malariakur durch Bacillus enteritidis Gärtner entstandene Meningitis und Sepsis, Tohoku J. Exper. Med. **21**:466-504 (Sept. 22) 1933.

26. Valledor, T.; García Pérez, E., and Pedrera, J.: Meningitis purulenta a Salmonela Eastbourne en un lactante de tres meses, tratado con sulfadiazina. Evolucion curativa después de una recaída, Bol. Soc. cubana de pediat. **14**:413-429 (Aug.) 1942.

27. Storey, W. E.: Purulent Meningitis Complicating Paratyphoid Fever: Report of a Case with Recovery, J. M. A. Georgia **12**:472-474 (Dec.) 1938.

28. Katsampes, C. P., and Bradford, W. L.: Recovery from Salmonella (Panama) Meningitis in an Infant Treated with Sulfapyridine, J. Pediat. **16**:79-85 (Jan.) 1940.

Book Reviews

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann, M.D. Third edition. Price, $5.00. Pp. 516, with 103 text illustrations and 4 color plates. St. Louis: C. V. Mosby Company, 1944.

This is the third edition of this book to appear in eight years, the first appearing in 1936. The author has made some changes in this edition. They consist essentially of dividing the data into more chapters for emphasis and the inclusion of four new chapters dealing with psychogenic disturbances associated with heart disease, essential hypertension and disturbances in blood pressure and general systemic types of heart disease.

Since the handbook is intended for the use of students, who are in need of "succinct outlines," the reviewer is impressed by certain aspects of the presentation which fail in these objectives. There is a great tendency for repetition, which is surely not intended for emphasis. For example, on page 437 are found the following statements concerning the histamine test: "In a few minutes there normally develops a red spot which rises into a 1 cm. wheal surrounded by flares 2 cm. in diameter." "Within five minutes, in the presence of normal adequate superficial circulation, a 1 cm. wheal surrounded by a 2 cm. flare should develop." On page 73 is presented a photograph of a Boulitte oscillometer, and on page 433 is presented another photograph of the same instrument, in this instance in place on a leg. This seems unnecessarily repetitious when either illustration would suffice, and two photographs certainly suggest too much importance for an instrument of almost questionable value. On page 443 the author states that "Nicotinic acid and histamine base may be of benefit." One wonders the exact meaning of the vague term "histamine base." On page 435 the author states, in writing on a vasomotor test: "A positive reaction indicates that the coolness of a part was the result of a circulatory disturbance of spastic origin. If, on the other hand, there is no rise under these conditions, the low skin temperature must be the result of decreased peripheral circulation of an organic, anatomic, obstructive type of obliterative arterial disease." Such a statement is vague, suggesting that organic anatomic disease may not be associated with spastic and obstructive disease.

Periarteritis nodosa is included among the peripheral vascular diseases, while scleroderma, lupus erythematosus disseminatus, and dermatomyositis are not included. Periarteritis is no more a peripheral vascular disease than the diseases listed. The section on peripheral vascular diseases in general is presented too much from the surgical point of view. In fact, that section of the book is not presented very well as a whole, certainly not as well as the chapters on heart disease.

A considerable number of data, with detailed tables, are presented on the Schneider test for cardiovascular efficiency. Even though it is used by the military services, it is well known to be far from perfect. It would appear to be in order for one to deemphasize or at least present the subject with a critical attitude when writing a brief handbook for such medically immature minds as possessed by medical students. When they enter the military services as medical officers they can learn the test in a matter of minutes should it be necessary.

The emphasis given the "cold pressor" test as an index of the hypertensive diathesis seems to be unwarranted by the generally accepted ideas and experiences concerning its value. Only a treatise on hypertension should contain very much detailed discussion on the subject at this stage of its evaluation.

On page 72 there is a section on the oscillometer which leaves the impression that all oscillometers are shaped and constructed like the Boulitte oscillometer, which, of course, is untrue, even though most of them are fashioned after the Pachen oscillometer. Incidentally, the author speaks of an "aneroid" to which the needle is connected. Obviously, such a use of the term aneroid is incorrect, as the word is an adjective. Apparently the author is referring to the bellows within the housing of the aneroid oscillometer. The author apparently feels (page 72) that the oscillometer measures the mean blood pressure. It is well to point out that there is no oscillometer yet available that will measure the mean blood pressure. Such claims have been made, usually with reservations, but they are not correct. Such an instrument would have many applications if it were available.

To electrocardiography is assigned 45 pages. Obviously, it is impossible to present this subject in such a concise form. Like many other authors, the attempt is made to do this, but is followed by the usual failure. Patterns are presented for the student to memorize, without any explanations of the mechanism which is responsible for the abnormalities. This is an error. Medical students should learn the reasons for and the mechanisms concerned. A good philosophic dissertation on the clinical applications and limitations of the electrocardiograph, with illustrations, is in order in a handbook of this sort. In other words, the subject should be presented thoroughly from a basic point of view to medical students if the book is intended for source of study, or not at all. As previously stated, the author perpetuates an error found in all one volume books on heart disease and has failed to clarify a common deficiency of monographs on heart disease.

There are other examples of weakness in the handbook. It is impossible to discuss each one. The presentation of bundle branch block from the point of view of the medical student is certainly vague and inadequate. This would be particularly true if a person should be confronted with the subject for the first time and seek information in the handbook. Another example is the list of the "Unquestionable evidences of heart disease," presented on page 466, which does not include a definite pericardial friction rub as a sign of heart disease.

Although the handbook has reached a third edition, to the surprise of the reviewer, it cannot be heartily recommended. Furthermore, and unfortunately for the lazy or busy student, cardiovascular disease and its management cannot be effectively presented in a synopsis as one might present a literary classic. Misinterpretation due to excessive brevity may lead to serious clinical consequences.

Laboratory Methods of the United States Army. Fifth edition. Edited by James Stevens Simmons, B.S., M.D., Ph.D., D.P.H., Sc.D. (Hon.), Brigadier General, United States Army; Chief of the Preventive Medicine Service, Office of the Surgeon General, United States Army; Lecturer in Tropical Medicine, Army Medical School; and Cleon J. Gentzkow, M.D., Ph.D., Colonel, Medical Corps, United States Army; Commanding Officer, Deshon General Hospital, Butler Pennsylvania; formerly Chief of the Division of Chemistry and Physics, Army Medical School. Approved by the Surgeon General of the United States Army. Price $7.50. Pp. 823, with 103 engravings and 8 color plates. Philadelphia: Lea & Febiger, 1944.

The medical officers who served in the division of infectious diseases in laboratories of the United States Army during the war of 1917-1918 may remember the first edition of "Laboratory Methods of the United States Army," published in 1918. This was a small pocket manual of 256 pages, a true vade mecum for the laboratory worker. This fifth edition, of 823 pages, each of which is double the size of the page of the first edition, is a comprehensive laboratory manual. It is dedicated to the memory of Dr. George M. Sternberg, who was Surgeon General of the United States Army during the last decade of the nineteenth century.

The editors have enlisted the services of twenty-three contributors, all of them either officers in the army or closely related as consultants in special fields. The book is divided into eleven parts as follows: "Clinical Pathology," "Chemistry," "Mycology," "Bacteriology," "Rickettsiae and Filtrable Viruses," "Protozoology," "Helminthology," "Entomology," "Pathology," "Special Veterinary Laboratory Methods" and "Statistical Methods." Each of these parts has from one to twelve chapters, and usually several different authors have contributed to each part. While the descriptions of technic are brief and the interpretations of necessity are much condensed, for the most part the procedures are adequate for the medical officer in a laboratory service. Many chapters are followed by brief but adequate lists of references, which should stimulate further interest in special fields.

Special mention may be made of the chapter on the chemical examination of water, sewage and industrial waste, not usually found in a laboratory manual. This chapter, along with chapter 30, on the bacteriology of water and sewage, gives important methods for examination of these materials.

There is a complete chapter of thirty-eight pages on toxicologic methods. Part 3, on mycology, contains three chapters which, with the references, should prove very useful. It may be hoped that in future editions there will be an expansion of this part of the book.

Part 5 contains a chapter on rickettsias by Harry Plotz and a chapter on the filtrable viruses by John R. Paul. While both of these chapters are of necessity brief, they are up-to-date and contain real information on these important subjects.

As may be expected, the chapters in the parts on protozoology and helminthology are complete and of real importance.

Part 11, on statistical methods, is especially well done and should prove of use to the statistician.

While this book is of particular interest to the army officer, it doubtless will be found to be a popular addition to the library of any physician interested in laboratory medicine.

Clinical Significance of the Blood in Tuberculosis. By Gulli Lindh Muller, M.D. Price, $3.50. Pp. 516. New York: The Commonwealth Fund, 1943.

This book contains a critical review of the literature and detailed serial hematologic findings in 1,000 consecutive cases of pulmonary tuberculosis observed at the State Sanitorium at Rutland, Mass. The values stressed are the red and white blood cell counts, differential count, hemoglobin content, hematocrit reading and sedimentation rate. The various parts of the book include: (1) the physiology of the blood-forming organs and the cellular response to the tubercle bacillus; (2) changes in the circulating blood in tuberculosis; (3) the sedimentation rate; (4) clinical and hematologic data as measures of constitutional reaction; (5) the effect of therapeutic methods, exercise and certain complications on the hematologic picture and (6) examination of the blood.

The book is detailed enough to give the reader a comprehensive review of hematologic methods and interpretations, in which there have been such great advances in the last fifteen years. Included are numerous tables and charts and a bibliography of 604 references. It would have been helpful if the author had added summaries at the end of the chapters.

Phthisiologists will find the volume of great assistance in making more extensive and intelligent use of hematologic data in the treatment of tuberculosis.

Synopsis of Neuropsychiatry. By Lowell S. Selling, Sc.M., M.D., Ph.D., Dr.P.H. Price, $5.00. Pp. 473. St. Louis: C. V. Mosby Company, 1944.

The purpose of the author of this book appears to have been to collect the important contributions of the various schools of psychiatric nosology and therapy. An eclectic approach of this type to a subject as important as psychiatry is worthy but difficult, unless one shows more unusual powers of discrimination than is suggested by the hodgepodge contained in these pages.

The section on neurology offers little advantage in time saving over a standard text and has the disadvantage of any synopsis in that it handles inadequately the more complex syndromes. The part on mental disorders inadequately describes the various forms of mental illness and the terminology used for them. Instead the pet terminology, reaction type of subdivisions, and so forth, of various contemporary psychiatrists receive rather more recognition than is necessary. The frequent use of slang seems to this reviewer to have little place in a work of this type. It is not apparent that the use of this pseudosemantic jargon increases the accuracy of the descriptions.

Terapeutica des los grandes sindromes digestivos. Edited by C. B. Udaondo. Pp. 271, with 7 figures. Buenos Aires, 1943.

This modest, paper-bound book gives an informal summary of the methods used at the National Public Dispensary for Digestive Diseases in the medical and surgical treatment of all varieties of gastrointestinal disorders. Although it lacks an alphabetical index and attempts no critical appraisal of fundamental assumptions or statistical evaluation of results, the book is interesting as a readable account of prevailing theory and practice, for each of its eighteen chapters is written by a different specialist and numerous prescriptions are given, both medical and dietary.

Tropical Nursing: A Handbook for Nurses and Others Going Abroad. By A. L. Gregg. Second edition. Price, $3.00. Pp. 185. New York: Philosophical Library, 1944.

The little book is valuable to persons bound for tropical zones for two reasons. It gives excellent hints for the maintenance of health in the tropics and provides specific information about materials and equipment needed. The larger portion is devoted to brief, clear descriptions of the numerous tropical diseases together with notes on treatment designed especially to meet the need of nurses and lay persons. The material is well written, up-to-date and dependable. The book is to be recommended for the purpose for which it was written, namely, as a small handbook useful to almost every one going to the tropics. It would also serve well as a "Dispensary Handbook" in the tropics.

Die Blutersatzfrage im Felde. By Prof. Dr. A. Fonio. Price, 3.80 francs (Swiss). Pp. 48. Berne, Switzerland: Medizinischer Verlag Hans Huber, 1943.

This booklet consists of a collection of five lectures on the use of blood substitutes on the battlefield written by the professor of surgery at the University of Berne, who reviews the whole subject with emphasis on the problem in the Swiss army. With the exception of experiences of the German army in this field, most of the material discussed is well known to American physicians. The absence of specific references detracts from the value of the lectures.

Vascular Responses in the Extremities of Man in Health and Disease. By David I. Abramson. Price, $5. Pp. 412, with 59 illustrations. Chicago: University of Chicago Press, 1944.

In his preface the author states that this book is the result of a need for the collection between two covers of the information on the vascular responses in the extremities which has accumulated in widely scattered journals. He has accomplished his task in noteworthy fashion and has produced a comprehensive monograph, extensively documented, dealing with all phases of the subject. Methods and clinical applications are thoroughly dealt with, and anatomic, physiologic and pharmacologic information is interpreted in its relation to disease. The book should be valuable for reference.

Elimination Diets and the Patients' Allergies. By Albert H. Rowe, M.D. Price, $3.50. Pp. 256. Philadelphia: Lea & Febiger, 1944.

This is the second edition of a well known and useful book. The basic thesis of the author is that the use of cutaneous tests as a means of determining sensitizations to food is fallacious. Certainly this is the general experience. It follows, then, that other approaches are required to uncover the responsible foodstuffs. The Rowe elimination diets have long been helpful in this regard. Making allowance for a certain enthusiasm about the importance of foods in the production of symptoms, the book nevertheless is of value to all physicians and especially to allergists.

Symposium on Chronic Diseases. In Medical Clinics of North America. Pp. 291-524, with 44 figures. Philadelphia and London: W. B. Saunders Company, 1944.

This volume contains eighteen articles on chronic diseases of various kinds. Most of the authors are recognized authorities in their fields, and the general practitioner will be helped and stimulated by reading them. There is, however, no organic relationship between the various articles, nor are they for the most part comprehensive. There is a good deal of reiteration of common knowledge. There are a number of tables and figures and an index.